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Limitations of the Open Loop Gain Concept in Studies of Respiratory Control

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A steady state mathematical model was used to study the limitations of applying the open loop gain concept to the ventilatory control system. Open loop gain is a term used in the study of linear control systems and is an indicator of how well the controlled variable is regulated. The model contained descriptions of the O_2 and CO_2 control systems as well as their interactions. Disturbances to the system were modelled as occurring via inspired air, metabolic rate and ventilation. The ventilatory response to hypoxia was simulated for (a) hypocapnic hypoxia, (b) normocapnic hypoxia ($PaCO_2$ = 40 torr) and (c) hypercapnic hypoxia ($PaCO_2$ = 45 torr). The open loop gains of the O_2 and CO_2 loops were calculated at each operating point. In addition, the sensitivity of the controlled variable to disturbances to the loop were also compared. It was observed that open loop gain did not completely describe the characteristics of the ventilatory control system. This was due to the fact that the ventilatory system is nonlinear and the regulatory ability of the ventilatory system depends on the route of the disturbance, and (2) open loop gain ignores the interactions of the CO_2 and O_2 loops, which can be substantial.

Keywords—*Ventilatory control, Respiration models.*

INTRODUCTION

Regulation of arterial levels of O_2 and CO_2 (i.e., PaO_2 and $PaCO_2$) occur via powerful negative feedback systems which, in effect, sense PaO_2 and $PaCO_2$ via peripheral and central chemoreceptors and adjust the level of ventilation in response to perturbations in these blood gas levels. The O_2 and CO_2 control systems interact, since the slope of the CO_2 response line is a function of PaO_2, and the slope of the O_2 response line at any PaO_2 is affected by $PaCO_2$ (3). The regulatory ability of either the CO_2 or O_2 loop has been estimated by applying the concept of open loop gain (GL) to the respiratory system (2,6–13,16,17). For a linear system, the higher the value of GL, the greater the regulatory ability or effectiveness of the loop (14,15). However, the concept of open loop gain has a number of possible limitations when applied to the ventilatory control system, for example, the respiratory system is nonlinear (1,2,5), and open loop gain calculations ignore the effects of secondary inter-

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acting loops (15). Thus, although the concept of open loop gain has been applied to the study of the respiratory system in the context of steady state regulation, the consequences of its limitations have not been systematically examined.

To examine these issues, a nonlinear steady state model of the O_2-CO_2 control systems, based on the methods of Khoo *et al.* (7), was used. The ventilatory responses to increasing levels of hypoxia (P_IO_2 from 150 to 80 torr) were predicted for hypocapnic hypoxia ($PaCO_2$ allowed to decrease), normocapnic hypoxia ($PaCO_2$ maintained constant at 40 torr), and hypercapnic hypoxia ($PaCO_2$ maintained constant at 45 torr). At each operating point, the open loop gains for the O_2 and CO_2 loops (G_LO_2 and G_LCO_2, respectively) were calculated. Disturbances to the ventilatory system were modelled as occurring to the O_2 loop via changes in metabolic rate and inspired air ($\dot{V}O_2$ and P_IO_2, respectively), to the CO_2 loop via changes in metabolic rate and inspired air ($\dot{V}CO_2$ and P_ICO_2, respectively), and to the controller as a disturbance in ventilation ($\dot{V}E_d$). Sensitivities of the controlled variables to the disturbances were evaluated with and without consideration of the secondary loop. Sensitivity was defined as the change in an independent variable that resulted from a change in a disturbance. Thus, the sensitivity of PaO_2 to a disturbance in P_IO_2 was designated as $\Delta PaO_2/\Delta P_IO_2$. Other sensitivities examined were: $\Delta PaO_2/\Delta \dot{V}O_2$, $\Delta PaO_2/\Delta \dot{V}E_d$, $\Delta PaCO_2/\Delta P_ICO_2$, $\Delta PaCO_2/\Delta \dot{V}CO_2$, and $\Delta PaCO_2/\Delta \dot{V}E_d$. The open loop gains for both the O_2 and CO_2 loops were compared to the sensitivities for the respective loop, and the effects of the secondary interacting loop were directly assessed.

METHODS

A block diagram of the steady state model is shown in Fig. 1. The model contained control loops for both PaO_2 and $PaCO_2$. The inputs to the controller were $PaCO_2$,

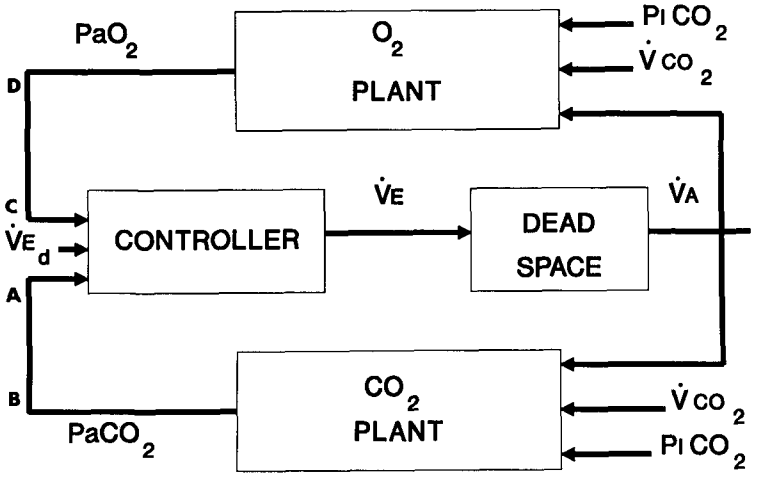

FIGURE 1. Block diagram of the model. The controller block (Eq. 1) has inputs $PaCO_2$, PaO_2, and $\dot{V}E_d$, which signifies a disturbance to ventilation. The output is $\dot{V}E$. The second block, labeled dead space (Eq. 4), describes the dependence of $\dot{V}A$ upon the input $\dot{V}E$. The O_2 plant is the gas exchanger for oxygen (Eq. 6) and relates the output PaO_2 to the inputs P_IO_2, $\dot{V}O_2$, and $\dot{V}A$. The CO_2 plant represents the exchange of carbon dioxide (Eq. 5) and relates the output $PaCO_2$ to the inputs P_ICO_2, $\dot{V}CO_2$ and $\dot{V}A$.

PaO_2, and $\dot{V}E_d$. The controller equation which described the relationship between $\dot{V}E$ and $PaCO_2$, PaO_2, and $\dot{V}E_d$ is given in Eq. 1, adapted from Khoo *et al.* (7) using the parameters for the awake sea level condition. It was assumed that ventilation increased linearly with increases in $PaCO_2$ and that the slope of this response increased with decreasing PaO_2. In addition, the ventilatory response to hypoxia was described as an exponential function. Thus, the interaction of the O_2 and CO_2 responses were modelled by the equation. $\dot{V}E_d$ was used to signify a disturbance to the present level of ventilation. Thus, $\dot{V}E_d$ could represent any change in $\dot{V}E$ due to mechanisms other than $PaCO_2$ and PaO_2.

$$\dot{V}E = G_p \exp(-0.05PaO_2)(PaCO_2 - I_p) + G_c(PaCO_2 - I_c) + \dot{V}E_d \tag{1}$$

where G_p and G_c are the peripheral and central chemoreceptor gains, respectively, and I_p and I_c are the peripheral and central thresholds, respectively.

The controller function was followed by an empirical description for the dependence of dead space on the level of ventilation and respiratory pattern (Eq. 2) (1,2,4). Breathing frequency was assumed to be a linear function of $\dot{V}E$ (Eq. 3), and the relationship between $\dot{V}E$ and $\dot{V}A$ is given in Eq. 4.

$$\dot{V}A = (1 - KDS)\dot{V}E - f VDS_0 \tag{2}$$

$$f = f_0 + K_f \dot{V}E. \tag{3}$$

Equations 2 and 3 can be combined to yield:

$$\dot{V}A = (1 - KDS - K_f VDS_0)\dot{V}E - f_0 VDS_0 \tag{4}$$

where $\dot{V}A$ is alveolar ventilation; KDS and VDS_0 are the slope and intercept, respectively, of the dead space tidal volume relationship; K_f and f_0 are the slope and intercept, respectively, of the $f - \dot{V}E$ relationship. Equations 2–4 are described in greater detail in an earlier study (1) and the same parameter values have been used.

The blocks for the plants (or controlled systems) of the O_2 and CO_2 control loops represent the appropriate mass balance equations, which assumed equilibrium across the alveolar-capillary membrane, i.e., $PACO_2 = PaCO_2$ and $PAO_2 = PaO_2$ (Eqs. 5 and 6). $PICO_2$, $\dot{V}CO_2$ and PIO_2, $\dot{V}O_2$ were viewed as inputs to the CO_2 and O_2 gas exchangers, respectively.

$$PaCO_2 = PICO_2 + \frac{863 \cdot \dot{V}CO_2}{\dot{V}A} \tag{5}$$

$$PaO_2 = PIO_2 - \frac{863 \cdot \dot{V}O_2}{\dot{V}A} \tag{6}$$

where $PICO_2$ and PIO_2 are inspired partial pressure of carbon dioxide and oxygen, respectively, $\dot{V}CO_2$ is CO_2 production rate, and $\dot{V}O_2$ is O_2 consumption rate.

Thus, the independent variables are $PICO_2$, PIO_2, $\dot{V}CO_2$, $\dot{V}O_2$, and $\dot{V}E_d$; and the dependent variables are $\dot{V}E$, $\dot{V}A$, $PaCO_2$, and PaO_2. For any set of independent variables and parameters, the values of the dependent variables can be obtained using a Newton-Raphson algorithm (1,2).

The open loop gain for the O_2 and CO_2 loops can be obtained by calculating the negative of the products of the slope of each element in the appropriate loop (14). For example,

$$G_LO_2 = -\frac{\partial \dot{V}_E}{\partial PaO_2}\frac{\partial \dot{V}_A}{\partial \dot{V}_E}\frac{\partial PaO_2}{\partial \dot{V}_A} \tag{7}$$

$$= (.05 \exp(-0.05PaO_2)G_p(PaCO_2 - I_p))(1 - K_{DS} - V_{DS_0}K_f)\left(\frac{863 \cdot \dot{V}_{O_2}}{\dot{V}_A{}^2}\right) \tag{8}$$

and

$$G_LCO_2 = -\frac{\partial \dot{V}_E}{\partial PaCO_2}\frac{\partial \dot{V}_A}{\partial \dot{V}_E}\frac{\partial PaCO_2}{\partial \dot{V}_A} \tag{9}$$

$$= (G_p \exp(-0.05PaO_2) + G_c)(1 - K_{DS} - V_{DS_0}K_f)\left(\frac{863 \cdot \dot{V}_{CO_2}}{\dot{V}_A{}^2}\right). \tag{10}$$

As can be seen from Eqs. 8 and 10, both G_LCO_2 and G_LO_2 are not constant but are nonlinear functions of the operating point ($\dot{V}_E$, $\dot{V}_A$, $PaCO_2$, PaO_2). In particular, the slopes of the controller function and plant function vary with the operating point. The slope of the relationship between $\dot{V}_A$ and $\dot{V}_E$ is assumed constant for these simulations.

The open loop gain (G_L) is indicative of the regulatory ability of a linear control system. A greater value of G_L would indicate a greater regulatory ability (14,15). However, G_L has some limitations in the context of respiratory control since the system is nonlinear and there are two control loops, the O_2 and CO_2 loops, which interact. First, implicit in the derivation of the open loop gains is the assumption that the second loop does not affect the first loop (15). Thus, with respect to Fig. 1, it is as if the control loops are opened between A-B for the CO_2 loop and C-D for the O_2 loop. An equivalent method of calculating G_LCO_2 would be to apply a signal $\Delta PaCO_2(A)$ at A and measure the response at B, $\Delta PaCO_2(B)$. The open loop gain is then $\Delta PaCO_2(B)/\Delta PaCO_2(A)$ (14). $\Delta PaCO_2(A)$ introduced at A would produce a change in $\dot{V}_E$ and thus $\dot{V}_A$, which would in turn change PaO_2. Note that if both loops are open, the change in PaO_2 would not feed back to the controller and affect $\dot{V}_E$. Thus, the concept of open loop gain does not take into account interactions between multiple control loops. The second limitation of open loop gain is that it does not always accurately reflect the ability of a nonlinear control system to regulate the controlled variable in response to variations in certain inputs (2).

To overcome these limitations, a set of sensitivities were calculated. They reflect the sensitivity of the controlled variable, either PaO_2 or $PaCO_2$, to changes in an independent variable, P_ICO_2, P_IO_2, $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$, or $\dot{V}_{E_d}$ (i.e., for the CO_2 loop, sensitivities are described as $\Delta PaCO_2/\Delta P_ICO_2$, $\Delta PaCO_2/\Delta \dot{V}_{CO_2}$, and $\Delta PaCO_2/\Delta \dot{V}_{E_d}$). These sensitivities can be calculated with or without inclusion of the interactions of the O_2 loop. A second group of sensitivities can be calculated for the O_2 loop with or without consideration of the influence of the CO_2 loop. The controller equation as well as the mass balance equations for O_2 and CO_2 is nonlinear. Following the methods of Riggs (15), these equations can be linearized and the resultant sensitivi-

ties calculated. The results indicate sensitivity of controlled variables to a very small change in independent variables around a particular operating point. Because of the nonlinear nature of the system, the open loop gains as well as the sensitivities will vary with the operating point, i.e., $\dot{V}_E$, $\dot{V}_A$, $PaCO_2$, or PaO_2. Thus, the equations for the independent variables can be written as:

$$PaO_2 = f_1(PIO_2, \dot{V}O_2, \dot{V}_A) \tag{11}$$

$$PaCO_2 = f_2(PICO_2, \dot{V}CO_2, \dot{V}_A) \tag{12}$$

$$\dot{V}_E = f_3(PaO_2, PaCO_2, \dot{V}_{E_d}) \tag{13}$$

$$\dot{V}_A = f_4(\dot{V}_E). \tag{14}$$

By linearizing these equations about an operating point, changes in the independent variables can be obtained (15) from:

$$\Delta PaO_2 = B_{11}\Delta PIO_2 + B_{12}\Delta\dot{V}O_2 + B_{13}\Delta\dot{V}_A \tag{15}$$

$$\Delta PaCO_2 = B_{21}\Delta PICO_2 + B_{22}\Delta\dot{V}CO_2 + B_{23}\Delta\dot{V}_A \tag{16}$$

$$\Delta\dot{V}_E = B_{31}\Delta PaO_2 + B_{32}\Delta PaCO_2 + B_{33}\Delta\dot{V}_{E_d} \tag{17}$$

$$\Delta\dot{V}_A = B_{41}\Delta\dot{V}_E \tag{18}$$

where

$$B_{11} = \partial f_1/\partial PIO_2, \quad B_{12} = \partial f_1/\partial\dot{V}O_2, \quad B_{13} = \partial f_1/\partial\dot{V}_A \tag{19}$$

$$B_{21} = \partial f_2/\partial PICO_2, \quad B_{22} = \partial f_2/\partial\dot{V}CO_2, \quad B_{23} = \partial f_2/\partial\dot{V}_A \tag{20}$$

$$B_{31} = \partial f_3/\partial PaO_2, \quad B_{32} = \partial f_3/\partial PaCO_2, \quad B_{33} = \partial f_3/\partial\dot{V}_{E_d} \tag{21}$$

$$B_{41} = \partial f_4/\partial\dot{V}_E. \tag{22}$$

Hence, Eqs. 8 and 10 for the open loop gains can be rewritten as:

$$G_LCO_2 = -B_{23}B_{41}B_{32} \tag{23}$$

and

$$G_LO_2 = -B_{13}B_{41}B_{31}. \tag{24}$$

One example, the sensitivity $S_1 = \Delta PaO_2/\Delta PIO_2$ ignoring the effects of the CO_2 loop, will be derived. The remaining sensitivities and the formulas used to calculate each sensitivity are summarized in Table 1. Ignoring the effects of the CO_2 loop means that $\Delta PaCO_2 = 0$. Substituting Eq. 18 into Eq. 15, assuming $\Delta\dot{V}O_2 = 0$, gives:

$$\Delta PaO_2 = B_{11}\Delta PIO_2 + B_{13}B_{41}\Delta\dot{V}_E. \tag{25}$$

TABLE 1. Definition of sensitivities.

	Without Secondary Loop	With Secondary Loop
$S_1 = \frac{\Delta PaO_2}{\Delta PIO_2}$	$\frac{1}{1 + GLO_2}$	$\frac{1 + GLCO_2}{1 + GLO_2 + GLCO_2}$
$S_2 = \frac{\Delta PaO_2}{\Delta \dot{V}O_2}$	$-\frac{863}{\dot{V}A(1 + GLO_2)}$	$-\frac{863(1 + GLCO_2)}{\dot{V}A(1 + GLO_2 + GLCO_2)}$
$S_3 = \frac{\Delta PaO_2}{\Delta \dot{V}E_d}$	$\frac{863 \cdot \dot{V}O_2B_{41}}{\dot{V}A^2(1 + GLO_2)}$	$\frac{863 \cdot \dot{V}O_2B_{41}}{\dot{V}A^2(1 + GLCO_2 + GLO_2)}$
$S_4 = \frac{\Delta PaCO_2}{\Delta PICO_2}$	$\frac{1}{1 + GLCO_2}$	$\frac{1 + GLO_2}{1 + GLCO_2 + GLO_2}$
$S_5 = \frac{\Delta PaCO_2}{\Delta \dot{V}CO_2}$	$\frac{863}{\dot{V}A(1 + GLCO_2)}$	$\frac{863(1 + GLO_2)}{\dot{V}A(1 + GLCO_2 + GLO_2)}$
$S_6 = \frac{\Delta PaCO_2}{\Delta \dot{V}E_d} = -\frac{863 \cdot \dot{V}CO_2B_{41}}{\dot{V}A^2(1 + GLCO_2)}$		$-\frac{863 \cdot \dot{V}CO_2B_{41}}{\dot{V}A^2(1 + GLCO_2 + GLO_2)}$
where $B_{41} = 1 - KDS - \dot{V}DS_0K_f$		

Remembering that $\Delta PaCO_2 = 0$ and assuming $\Delta \dot{V}E_d = 0$, Eq. 17 is substituted into Eq. 25, which yields:

$$\Delta PaO_2 = B_{11}\Delta PIO_2 + B_{13}B_{41}B_{31}\Delta PaO_2; \tag{26}$$

rearranging, yields:

$$\frac{\Delta PaO_2}{\Delta PIO_2} = \frac{B_{11}}{1 - B_{13}B_{41}B_{31}} = \frac{1}{1 + GLO_2}, \tag{27}$$

since $B_{11} = 1$.

The ventilatory responses were predicted for decreasing levels of PIO_2 between 150 and 80 torr for three conditions: (a) $PaCO_2$ was allowed to decrease (hypocapnic hypoxia), (b) $PaCO_2$ was maintained constant at the normal resting value of 40 torr (normocapnic hypoxia), and (c) $PaCO_2$ was maintained constant at the hypercapnic value of 45 torr (hypercapnic hypoxia). For each predicted operating point the open loop gains and sensitivities were calculated. By comparing the predictions for conditions b and c, the effects of an increase in $PaCO_2$ upon the regulatory properties of the respiratory system can be discerned for any value of PaO_2. To simulate isocapnic conditions, $PaCO_2$ in Eq. 1 can be set equal to either 40 or 45 torr, and Eq. 5 can be ignored when solving for the new operating point. When calculating $GLCO_2$ (Eq. 10) it was assumed that $\dot{V}CO_2$ had not changed. Therefore, we implicitly assumed that $PaCO_2$ during hypoxia was maintained at isocapnic levels by altering $PICO_2$, although this does not have to be done by explicitly changing $PICO_2$ in Eq. 5.

RESULTS

CO_2 loop gain

The predicted behavior of the open loop gain of the CO_2 loop (G_LCO_2) for the three progressive hypoxic conditions is shown in Fig. 2 as a function of the predicted steady state PaO_2. For the hypocapnic response to hypoxia, ventilation increased with decreases in PaO_2, which in turn led to decreases in $PaCO_2$. G_LCO_2 increased approximately threefold with decreasing PaO_2. However, if $PaCO_2$ was maintained during hypoxia at the normocapnic value (40 torr), G_LCO_2 was predicted to decrease with increasing levels of hypoxia. Increasing $PaCO_2$ to 45 torr resulted in a further decrease in G_LCO_2 at all levels of PaO_2. Thus, these predictions suggest that the regulatory ability of the CO_2 loop was improved during hypocapnic hypoxia but was reduced during isocapnic hypoxia. For any value of PaO_2, the effect of increasing $PaCO_2$ was to lower G_LCO_2.

G_LCO_2 is equal to the negative product of the slopes around the CO_2 loop; i.e., $G_LCO_2 = -B_{23}B_{32}B_{41}$, where $B_{23} = \partial PaCO_2/\partial \dot{V}A$ is the slope of the CO_2 plant function, $B_{32} = \partial \dot{V}E/\partial PaCO_2$ is the slope of the controller function with respect to $PaCO_2$, and B_{41} is the slope of the dead space relationship and was assumed constant for these simulations. To gain further insight into the factors affecting G_LCO_2, Fig. 2 also shows B_{23} and B_{32}. B_{32} was a unique function of PaO_2 and increased monotonically with decreasing PaO_2. This simply represents the augmentation of the CO_2 gain by hypoxia. However, B_{23} depends on the $PaCO_2$ as well as the level of $\dot{V}A$, since B_{23} can be written as:

$$B_{23} = \frac{\partial f_2}{\partial \dot{V}A} = \frac{863\dot{V}CO_2}{\dot{V}A^2} = \frac{PaCO_2 - PiCO_2}{\dot{V}A}. \tag{28}$$

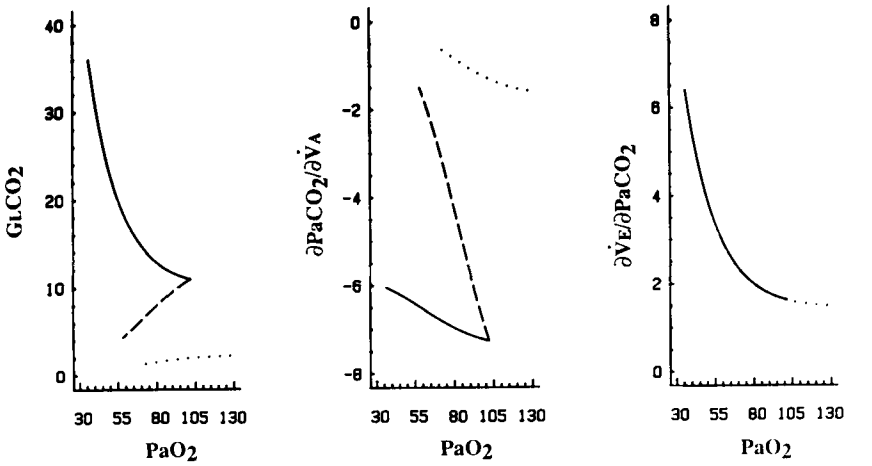

FIGURE 2. Open loop gain of the carbon dioxide loop. The open loop gain of the CO_2 loop (G_LCO_2), the slope of the CO_2 plant function ($B_{23} = \partial PaCO_2/\partial \dot{V}A$), and the slope of the controller function with respect to $PaCO_2$ ($B_{32} = \partial \dot{V}E/\partial PaCO_2$) are plotted versus the predicted PaO_2 for hypocapnic hypoxia (solid lines; ——), normocapnic hypoxia (dashed lines; – – –), and hypercapnic hypoxia (dotted lines; · · ·). PiO_2 was varied between 80 and 150 torr for each of the three hypoxic conditions.

For hypocapnic hypoxia the magnitude of B_{23} decreased with hypoxia. G_LCO_2 increased since the increase in B_{32} was greater than the decrease in B_{23}. However, for isocapnic hypoxia, $PaCO_2 = 40$ torr, B_{23} decreased to a much greater degree and the net result was a decrease in G_LCO_2. Increasing $PaCO_2$ to 45 torr caused a further decrease in B_{23} and thus a further decrease in G_LCO_2 for any level of PaO_2. Therefore, the differences in the predicted behavior of G_LCO_2 between the three hypoxic conditions resulted primarily from changes in the plant characteristics and not from the controller, since the slope of the controller function was a unique function of PaO_2.

O_2 loop gain

For hypocapnic hypoxia, G_LO_2 increased by a factor of approximately six, suggesting that the regulatory ability of the O_2 loop improved with progressive hypoxia (Fig. 3). For normocapnic hypoxia ($PaCO_2 = 40$ torr), G_LO_2 increased slightly with decreasing PaO_2 and reached a peak at a PaO_2 of approximately 65 torr. Thereafter, G_LO_2 decreased slightly with further decreases in PaO_2. For hypercapnic hypoxia ($PaCO_2 = 45$ torr), G_LO_2 was decreased relative to both hypocapnic hypoxia and normocapnic hypoxia but did increase slightly with progressive hypoxia. Thus, it would appear that maintaining $PaCO_2$ constant during hypoxia degraded the regulatory ability of the O_2 loop. Also, hypercapnia further degraded the regulatory ability of the O_2 loop at any value of PaO_2.

The predicted behavior of G_LO_2 for the three hypoxic conditions can be explained by changes in both the plant and controller characteristics. G_LO_2 is equal to the negative product of the slopes around the O_2 loop; i.e., $G_LO_2 = -B_{13}B_{31}B_{41}$, where $B_{13} = \partial PaO_2/\partial \dot{V}A$ is the slope of the O_2 plant function, $B_{31} = \partial \dot{V}E/\partial PaO_2$ is the slope of the controller function with respect to PaO_2, and B_{41} is the slope of the dead space

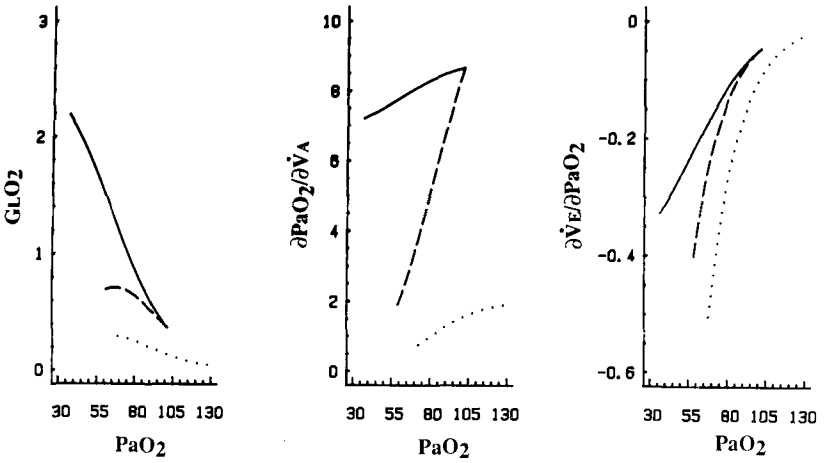

FIGURE 3. Open loop gain of the oxygen loop. The open loop gain of the O_2 loop (G_LO_2), the slope of the O_2 plant function ($B_{13} = \partial PaO_2/\partial \dot{V}A$), and the slope of the controller function with respect to PaO_2 ($B_{31} = \partial \dot{V}E/\partial PaO_2$) are plotted versus the predicted PaO_2 for hypocapnic hypoxia (solid lines; ——), normocapnic hypoxia (dashed lines; – – –), and hypercapnic hypoxia (dotted lines; · · ·). PIO_2 was varied between 80 and 150 torr for each of the three hypoxic conditions.

function. The magnitude of B_{31} increased with decreasing values of PaO_2, and at a particular value of PaO_2 was further augmented by increases in $PaCO_2$. The magnitude of B_{13} decreased slightly during hypocapnic hypoxia. This decrease was offset by the increase in B_{31}, and G_LO_2 increased substantially. Maintaining $PaCO_2$ constant during hypoxia at the normocapnic value greatly decreased B_{13} at any value of PaO_2. Thus, although maintaining $PaCO_2$ constant at 40 torr increased the magnitude of B_{31}, the decrease in B_{13} was such that the increase in G_LO_2 during hypoxia was substantially reduced. Increasing $PaCO_2$ during hypoxia to 45 torr further decreased B_{13} and, thus, G_LO_2. Therefore, the predicted increase in G_LO_2 during hypocapnic hypoxia was due primarily to characteristics of the controller function; whereas, the predicted decreased in G_LO_2 resulting from maintaining $PaCO_2$ constant at either normocapnic or hypercapnic values was due primarily to the characteristics of the O_2 plant function, i.e., the gas exchange process.

Regulation of PaO_2

The regulation of PaO_2 in response to disturbances in either P_IO_2, $\dot{V}O_2$, or $\dot{V}_E$ are shown in Fig. 4, with and without consideration of the CO_2 loop. First, the sensitivities ignoring the effects of the CO_2 loop will be discussed. Consistent with the earlier predictions (Fig. 3) that G_LO_2 increased with decreasing levels of PaO_2 for all three hypoxic conditions, thereby suggesting an improved regulatory ability, the mag-

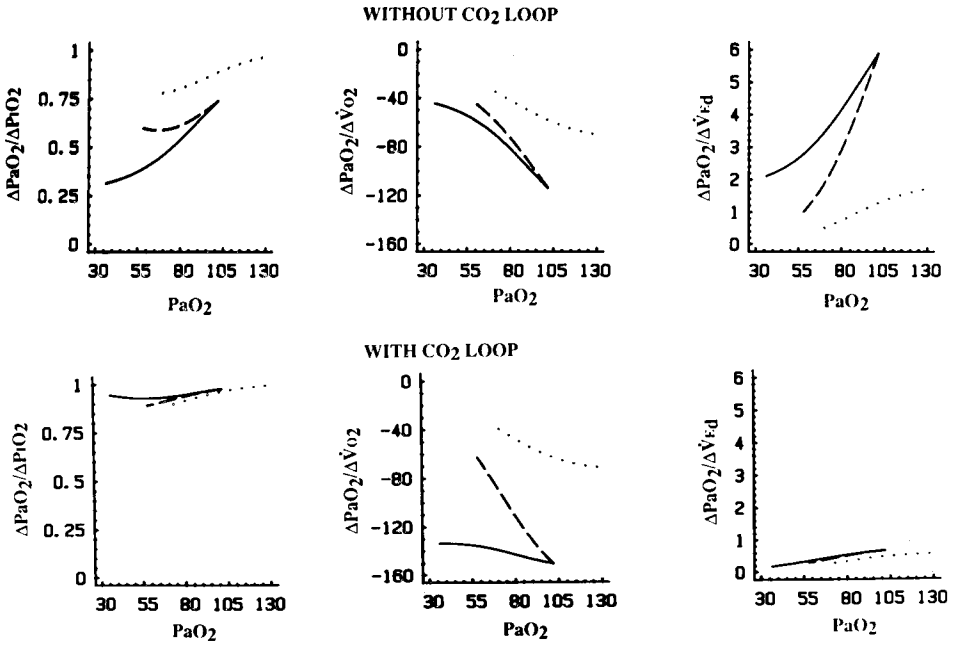

FIGURE 4. Regulation of PaO_2. The sensitivities $S_1 = \Delta PaO_2/\Delta PIO_2$, $S_2 = \Delta PaO_2/\Delta \dot{V}O_2$, and $S_3 = \Delta PaO_2/\Delta \dot{V}E_d$ are plotted against the predicted value of PaO_2 for hypocapnic hypoxia (solid lines; ——), normocapnic hypoxia (dashed lines; – – –), and hypercapnic hypoxia (dotted lines; · · ·). The upper row of graphs are the sensitivities when the secondary effects due to the CO_2 loop are ignored, and the lower row represents the predicted sensitivities when the effects of the CO_2 loop are included.

nitude of the sensitivities S_1 ($\Delta PaO_2/\Delta PIO_2$), S_2 ($\Delta PaO_2/\Delta \dot{V}O_2$), and S_3 ($\Delta PaO_2/\Delta \dot{V}E_d$) all decreased with increasing levels of hypoxia (Fig. 4) for the three conditions. Thus, the change in PaO_2 per unit change in either PIO_2, $\dot{V}O_2$, or $\dot{V}E_d$ would be less during hypoxia than during normoxia for the hypocapnic, normocapnic and hypercapnic conditions. Thus, GLO_2 does qualitatively reflect the change in regulatory ability of the O_2 loop with increasing levels of hypoxia. However, the effects of changing $PaCO_2$ during hypoxia on the regulatory characteristics of the O_2 loop is more complex. For any value of PaO_2, increasing $PaCO_2$ from hypocapnic to normocapnic to hypercapnic levels resulted in decreases in GLO_2 (Fig. 3), indicating decreased regulatory abilities of the O_2 loop. Consistent with this prediction, S_1 is increased at higher levels of $PaCO_2$ for any value of PaO_2. However, at any value of PaO_2, the magnitudes of S_2 and S_3 were decreased for increasing values of $PaCO_2$. Thus, at any level of PaO_2, increasing $PaCO_2$ reduced the regulatory ability of the O_2 loop to disturbances in PIO_2, but improved the regulatory ability of the loop to disturbances in either $\dot{V}O_2$ or $\dot{V}E_d$. Thus, the relationship between either S_2 or S_3 and GLO_2 was rather complex and GLO_2 did not provide a complete description of the regulatory ability of the O_2 loop, even when the influence of the CO_2 loop was ignored.

The interaction between the O_2 and CO_2 loops has substantial effects on the predicted behavior of S_1, S_2, and S_3. For both S_1 and S_2 the CO_2 loop acted to degrade the performance of the O_2 loop. For both S_1 and S_2 the degradation of performance was greatest for the hypocapnic hypoxia and least for hypercapnic hypoxia (Fig. 4). However, if the disturbance was introduced via $\dot{V}E_d$, the CO_2 loop acted to greatly improve the performance of the O_2 loop. The improvement in performance was approximately eightfold for the hypocapnic hypoxic condition. These results demonstrate the importance of including the effects mediated by the CO_2 loop in the regulation of PaO_2. Also, these results point out that the effects of the interaction of the O_2 and CO_2 loops on regulation of PaO_2 depend on the route of the disturbance. The inability of GLO_2 to completely describe the regulatory properties of the O_2 loop is apparent. It is concluded that GLO_2 does not adequately describe the regulatory properties of the O_2 loop since it does not always predict, even in a qualitative manner, the ability of the O_2 loop to regulate PaO_2 when disturbances are introduced via either metabolism or ventilation; it also ignores important interactions with the CO_2 loop.

Regulation of $PaCO_2$

The regulation of $PaCO_2$ in response to disturbances in either $PICO_2$, $\dot{V}CO_2$, and $\dot{V}E_d$ are shown in Fig. 5, with and without consideration of the O_2 loop. First, the predictions ignoring the O_2 loop will be discussed. Consistent with the prediction that $GLCO_2$ increases during hypocapnic hypoxia (Fig. 2), indicating an improved regulatory ability, the magnitudes of $S_4 = \Delta PaCO_2/\Delta PICO_2$, $S_5 = \Delta PaCO_2/\Delta \dot{V}CO_2$, and $S_6 = \Delta PaCO_2/\Delta \dot{V}E_d$ all decreased with decreases in PaO_2 during hypocapnic hypoxia. Thus, for hypocapnic hypoxia, the regulatory ability of the CO_2 loop improved for all three routes of disturbances for increasing levels of hypoxia. Maintaining $PaCO_2$ during hypoxia at the normocapnic value (40 torr) resulted in a predicted decrease in $GLCO_2$ (Fig. 2) and a corresponding increase in S_4. These predictions suggest an improvement in regulatory ability. However, for this normocapnic con-

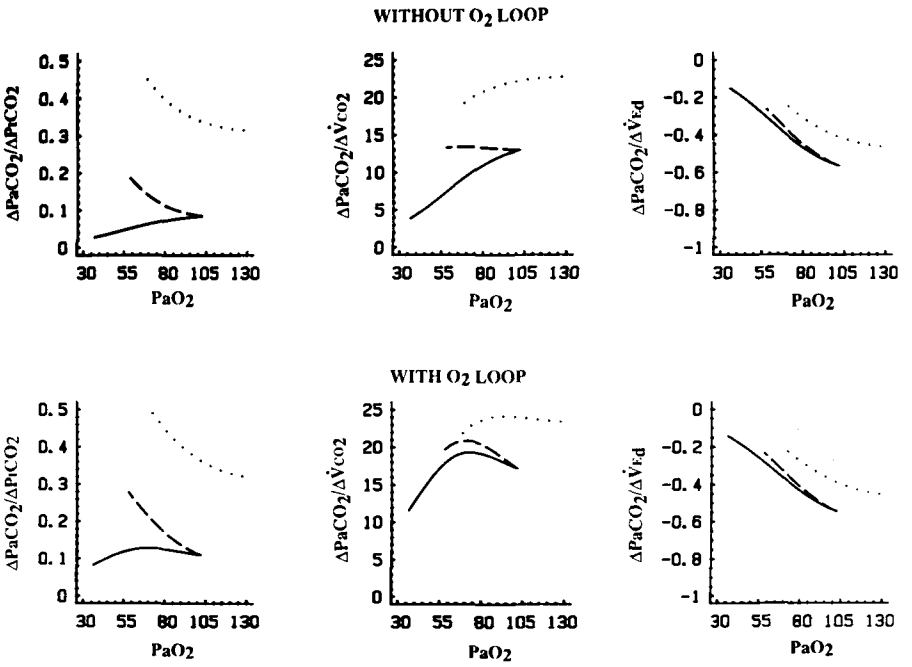

FIGURE 5. Regulation of $PaCO_2$. The sensitivities $S_4 = \Delta PaCO_2/\Delta PiCO_2$, $S_5 = \Delta PaCO_2/\Delta \dot{V}CO_2$, and $S_6 = \Delta PaCO_2/\Delta \dot{V}E_d$ are plotted against the predicted value of PaO_2 for hypocapnic hypoxia (solid lines; ——), normocapnic hypoxia (dashed lines; – – –), and hypercapnic hypoxia (dotted lines; · · ·). The upper row of graphs are the sensitivities when the influence of the O_2 loop is ignored, and the bottom row of graphs are the sensitivities when the effects of the O_2 loop are included.

dition, S_5 remained essentially constant and S_6 decreased with progressive hypoxia and did not follow the predicted change in $GLCO_2$. Thus, compared to hypocapnic hypoxia, the regulatory ability of the CO_2 loop during normocapnic hypoxia was degraded for disturbances via $PICO_2$ but improved for disturbances via $\dot{V}CO_2$ and remained unchanged for disturbances via $\dot{V}E_d$. For hypercapnic conditions, decreasing levels of PaO_2 caused a reduction in the predicted $GLCO_2$. There was a corresponding increase in S_4 with increasing levels of hypoxia. However, the magnitudes of S_5 and S_6 decreased with increasing levels of hypoxia. Therefore, for hypercapnic conditions, increasing levels of hypoxia decreased the regulatory ability of the CO_2 loop with regard to disturbances in $PICO_2$, but increased the regulatory ability of the loop with regard to disturbances via $\dot{V}CO_2$ and $\dot{V}E_d$. At any level of PaO_2, increasing $PaCO_2$ produced a decrease in $GLCO_2$ and corresponding increases in S_4 and S_5. However, the magnitude of S_6 decreased with increasing $PaCO_2$. Thus, hypercapnia decreases the regulatory ability of the CO_2 loop to disturbances in $PICO_2$ and $\dot{V}CO_2$ but improves the regulatory ability of the loop to disturbances in $\dot{V}E_d$. These results demonstrate that $GLCO_2$ does not completely describe the regulatory properties of the CO_2 loop.

The O_2 loop acted to substantially decrease the regulatory ability of the CO_2 loop when the disturbances were introduced via $PICO_2$ or $\dot{V}CO_2$. However, the O_2 loop acted to slightly improve the regulation of $PaCO_2$ when the disturbance was via $\dot{V}E_d$.

In all cases, the influence of the O_2 loop upon the CO_2 loop was the greatest at the lower values of PaO_2. By including the effect of the O_2 loop, the predicted values of S_4 and S_5 at the lowest PaO_2 increased by a factor of approximately 2.5. The monotonic decreases predicted for S_4 and S_5 when the O_2 loop was ignored were changed by the action of the O_2 loop to biphasic responses. There were initial increases followed at lower values of PaO_2 by decreases in the sensitivities. These results further suggest that the interaction of the secondary loop, the O_2 loop in this case, has substantial effects on the performance of the primary loop.

DISCUSSION

This study examined the regulatory properties of a steady state model of the oxygen and carbon dioxide ventilatory control systems. The model was composed of an O_2 loop and a CO_2 loop which interacted at the level of the controller. An important result of this simulation study was the prediction that the open loop gains, G_LCO_2 for the CO_2 loop and G_LO_2 for the O_2 loop, did not adequately describe the regulatory properties of the respiratory control system. There are two principal shortcomings of employing the open loop gain concept in the study of the respiratory system. First, open loop gain is a concept derived from the study of linear control systems (13,14) and cannot completely describe the properties of a nonlinear system. In the present context this is demonstrated most clearly by the predictions which show that the effects of hypoxia upon the ability of a control loop to regulate its controlled variable depend on the route of the disturbance and the operating point. Second, open loop gain does not take into account the possible interactions of the two loops (15). For example, it was demonstrated (Fig. 4) that the CO_2 loop could exert strong modulatory actions on the regulatory properties of the O_2 loop during hypoxia.

For the respiratory system, open loop gain is defined for a particular operating point, i.e., $\dot{V}_E$, PaO_2, and $PaCO_2$, and if the operating point is changed the value of the open loop gain will also change. However, the value of an open loop gain at a particular operating point may not be unique. In other words, for a particular set of values for $\dot{V}_E$, $PaCO_2$, and PaO_2, the value of the open loop gain at this operating point will depend on the inputs (e.g., P_ICO_2, P_IO_2, $\dot{V}o_2$, $\dot{V}co_2$) and parameters (e.g., G_p and G_c). There may be more than one set of parameters and inputs which would be consistent with a particular operating point and the open loop gain would be different for each. In this simulation study, disturbances were modelled as occurring via three routes: inspired air, metabolism, and ventilation. Ignoring for the moment loop interactions, open loop gain adequately described the regulatory ability of the loop for a disturbance introduced via inspired air but not to disturbances introduced via metabolism or ventilation. In other words, $S_1 = \Delta PaO_2/\Delta P_IO_2$ was a simple function of the open loop gains, whereas $S_2 = \Delta PaO_2/\Delta\dot{V}o_2$ and $S_3 = \Delta PaO_2/\Delta\dot{V}E_d$ also depend on $\dot{V}_A$ and $\dot{V}_A^2$, respectively (Table 1). Previous studies have shown that the open loop gain is a function of the operating point and varies with changes in inputs or parameters (13). However, the present study is the first to clearly show that open loop gain does not completely describe the regulatory properties of a nonlinear control loop. This is illustrated by the prediction that for any value of PaO_2, maintaining $PaCO_2$ at normocapnic levels during hypoxia decreased G_LO_2 and increased $S_1 = \Delta PaO_2/\Delta P_ICO_2$, which is consistent with a decreased regulatory ability. However, $S_2 = \Delta PaO_2/\Delta\dot{V}o_2$ and $S_3 = \Delta PaO_2/\Delta\dot{V}E_d$ were decreased, indicat-

ing an improved regulatory ability. Thus, under these circumstances open loop gain did not accurately predict the ability of the O_2 loop to regulate PaO_2 when the disturbances are introduced via metabolism or ventilation. Similar comments apply to the CO_2 loop.

The inability of the open loop gain to accurately reflect the regulatory ability of the system to disturbances in metabolism or ventilation has other possible consequences. Since CO_2 inhalation is an experimental condition and disturbances to the system via metabolism and ventilation most likely occur in normal settings, open loop gain might not provide a relevant indication of the regulatory ability of the system. It suggests further that CO_2 inhalation may not always be an appropriate method of assessing the ability of the control system to regulate $PaCO_2$.

This study has demonstrated the importance of considering loop interactions. The nature of the loop interactions depended on the route of the disturbance. For example, the CO_2 loop acted to increase the sensitivity of PaO_2 to disturbances introduced by either P_IO_2 or $\dot{V}O_2$ but decreased the sensitivity of PaO_2 to a disturbance by $\dot{V}E_d$. Similar comments apply to the effect of the O_2 loop on the CO_2 loop. Thus, the O_2 loop and CO_2 loop worked in opposition when the disturbance to the respiratory system was via inspired air or metabolism; whereas, the loops worked in a complementary fashion if the disturbance was by ventilation. Therefore, it is important to consider the route of the disturbance when discussing the regulatory properties of the respiratory system. For all conditions studied, the CO_2 loop greatly affected the regulatory ability of the O_2 loop as evidenced by the substantial difference in the magnitudes of S_1, S_2, and S_3 when comparing the predictions of the O_2 loop acting alone with the predictions for the loops interacting (Fig. 4). Quantitatively, the O_2 loop had relatively minor effects on the regulatory ability of the CO_2 loop during normoxia, but the effects became more substantial with hypoxia.

Due to the nonlinearities of the respiratory system and the interactions between the O_2 and CO_2 loops, the regulatory ability of the respiratory control system is best described as a series of sensitivities which describe the change in a controlled variable ($PaCO_2$ or PaO_2) to a small disturbance (P_ICO_2, P_IO_2, $\dot{V}CO_2$, $\dot{V}O_2$, or $\dot{V}E_d$ in the present study). These sensitivities can be derived in a way that takes into account loop interactions. As noted above, the open loop gains and sensitivities are functions of the operating point. Thus, in order to describe the regulatory characteristics of the respiratory system, the resting operating point ($PaCO_2$, PaO_2, $\dot{V}E$) as well as the metabolic rate and controller functions must be specified. The sensitivity functions can then be calculated for various inputs or changes in parameters permitted by the model. For example, if one desired to examine the effects of a drug infusion on the regulatory properties of the respiratory control system, it would be necessary to determine the metabolic rates, operating point, and controller function before and after the drug infusion. The sensitivities could be calculated for the two conditions and compared. The techniques described herein could be applied to alternative or more complex models of the respiratory system. Additional sensitivities could also be calculated, e.g., $\Delta PaO_2/\Delta VDS$, where VDS is dead space volume. Therefore, these techniques represent a systematic method of quantitatively examining regulatory properties of the nonlinear respiratory control system.

At the normoxic eucapnic operating point, $GLCO_2$ was predicted to be 10.96. This value is lower than the value predicted in an earlier study (2; $GLCO_2 = 23.8$) due to the difference in the assumed values for the slope of CO_2 response line. How-

TABLE 2. Predicted sensitivities at the normal operating point.

Sensitivity	Units	Without Secondary Loop	With Secondary Loop
S_1	torr/torr	0.734	0.971
S_2	torr/l/min	−114.0	−150.7
S_3	torr/l/min	5.904	0.652
S_4	torr/torr	0.084	0.110
S_5	torr/l/min	12.98	17.15
S_6	torr/l/min	−0.564	−0.547
$G_{LO_2} = 0.362$			
$G_{LCO_2} = 10.96$			

ever, both these predictions fall within the values obtained experimentally (6,11,12). The value of G_{LO_2} was predicted to be 0.362 for the normal operating point and is slightly less than the values obtained experimentally (10; $G_{LO_2} = 0.5$ to 5.0). That G_{LCO_2} was predicted to be substantially greater than G_{LO_2} agrees with experimental results obtained in human subjects (12) and suggests that the CO_2 control loop is a better regulator than the O_2 loop. Comparison of Figs. 2 and 3 indicates that the primary reason for this difference between the loop gains of the O_2 and CO_2 loops was due to the controller function, i.e., $B_{32} = \partial \dot{V}E/\partial PaCO_2 = 1.62$ l/min/torr but $B_{31} = \partial \dot{V}E/\partial PaO_2 = -0.045$ l/min/torr for the normoxic eucapnic control point. Even at a $P_IO_2 = 80$ torr, where $PaCO_2$ and PaO_2 were predicted to be 36.8 and 36.1 torr, respectively, B_{32} increased to 6.41 l/min/torr while B_{31} increased to only −0.328 l/min/torr. That the CO_2 loop may be a better regulator than the O_2 loop is also supported by predictions that, when ignoring the effect of the second loop, S_1 was greater than S_4, S_2 was greater than S_5, and S_3 was greater than S_6 (Table 2).

In summary, this simulation study has demonstrated that, in the context of steady-state regulation, the concept of open loop gain has serious limitations when applied to nonlinear systems, especially those with multiple interacting control loops. It was also shown that the regulatory ability of a control loop of a nonlinear system will depend on the specific operating point, the actions of any other interacting loops, and the route of the disturbance. With regard to this latter point, the present study extends the results of a previous study (2) which suggested that G_{LCO_2} did not adequately describe the regulatory properties of the CO_2 loop even when considered in isolation from the O_2 loop. Although this report did not investigate the use of open loop gain in studies of the stability of the respiratory system (7), it raises the possibility that similar limitations to those discussed here may apply.

REFERENCES

1. Bennett, F.M.; Fordyce, W.E. Gain of the ventilatory exercise stimulus: definition and meaning. J. Appl. Physiol. 65:2011-2017; 1988.
2. Bennett, F.M.; Fordyce, W.E. Regulation of $PaCO_2$ during rest and exercise: a modelling study. Submitted J. Appl. Physiol.
3. Cunningham, D.J.C.; Robbins, P.A.; Wolff, C.B. Integration of respiratory responses to changes in alveolar partial pressures of CO_2 and O_2 and in arterial pH. In: Handbook of physiology. The respiratory system. Vol. II. Control of breathing. Part 2. Bethesda, Md.; 1986: pp. 475-528.

4. Gray, J.S.; Grodins, F.S.; Carter, E.T. Alveolar and total ventilation and the dead space problem. J. Appl. Physiol. 9:307–320; 1956.
5. Grodins, F.S.; Gray, J.S.; Schroeder, K.R.; Norins, A.L.; Jones, R.W. Respiratory responses to CO_2 inhalation. A theoretical study of a non-linear biological regulator. J. Appl. Physiol. 7:283–308; 1954.
6. Honda, Y.; Hayashi, F.; Yoshida, A.; Ohyabu, Y.; Nishibayashi, Y.; Kimura, H. Overall "gain" of the respiratory control system in normoxic humans awake and asleep. J. Appl. Physiol. 55:1530–1535; 1983.
7. Khoo, M.C.K.; Kronauer, R.E.; Strohl, K.P.; Slutsky, A. Factors inducing periodic breathing in humans: a general model. J. Appl. Physiol. 53:644–659, 1982.
8. Loeschcke, H.H. The respiratory control system: analysis of steady state solutions for metabolic and respiratory acidosis-alkalosis and increased metabolism. Pflugers Arch. 341:23–42; 1973.
9. Loeschcke, H.H. The effectiveness of the control of pH in the extracellular fluid of the brain by the respiratory control system. Pflugers Arch. 341:43–50; 1973.
10. Masuyama, H.; Hayashi, F.; Honda, Y. An assessment of overall "gain" of the O_2 feedback control system with and without external dead space breathing. Jpn. J. Physiol. 33:699–710; 1983.
11. Masuyama, H.; Honda, Y. Difference in overall "gain" of CO_2 feedback system between dead space and CO_2 ventilation in man. Bull. Eur. Physiopathol. Respir. 20:501–506; 1984.
12. Masuyama, H.; Akiyama, S.; Honda, Y. An assessment of overall open-loop "gain" of CO_2 ventilation feedback control system in hypoxia. Jpn. J. Physiol. 35:545–552; 1985.
13. Milhorn, H.T., Jr.; Guyton, A.C. An analog computer analysis of Cheyne-Stokes breathing. J. Appl. Physiol. 20:328–333; 1965.
14. Milhorn, H.T., Jr. The application of control theory to physiological systems. Philadelphia, Pa.: Saunders; 1966.
15. Riggs, D.S. Control theory and physiological feedback mechanisms. Huntington, New York: R.E. Krieger Publishing Co.; 1976.
16. Stegemann, J.; Seez, P.; Kremer, W.; Boning, D. A mathematical model of the ventilatory control system to carbon dioxide with special reference to athletes and nonathletes. Pflugers Arch. 356:223–236; 1975.
17. Takano, N.; Sakai, A.; Iida, Y. Analysis of alveolar P_{CO_2} during the menstrual cycle. Pflugers Arch. 390:56–62; 1981.