A MATHEMATICAL MODEL OF THE CONTROLLED PLANT OF THE RESPIRATORY SYSTEM

T. J. TRUEB, N. S. CHERNIACK, A. F. D'SOUZA, *and* A. P. FISHMAN

From the Cardiovascular-Pulmonary Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, and the Department of Mechanical and Aerospace Engineering, Illinois Institute of Technology, Chicago, Illinois 60616

ABSTRACT Ability to predict the dynamic response of oxygen, carbon dioxide tensions, and pH in blood and tissues to abrupt changes in ventilation is important in the mathematical modeling of the respiratory system. In this study, the controlled plant (the amount and distribution of O_2 and CO_2) of the respiratory system is modeled. Although the body tissues are divided into a finite number of "compartments" (three tissue groups), in contrast to earlier models, the blood and tissue gas tensions within each compartment are considered to be continuously distributed in time and in one spatial coordinate. The mass conservation equations for oxygen and carbon dioxide involved in the blood-tissue gas exchange are described by a set of partial differential equations which take into account convection of O_2 and CO_2 caused by the flow of blood as well as diffusion due to local tension gradients. Nonlinear algebraic equations for the dissociation curves, which take into account the Haldane and Bohr effects in blood, are used to obtain the relationships between concentrations and partial pressures. Time-variable delays caused by the arterial and venous transport of the respiratory gases are also included. The model so constructed successfully reproduced actual O_2 and CO_2 tensions in arterial blood, and in muscle venous and mixed venous blood when ventilation was abruptly changed.

INTRODUCTION

Changes in the amount and distribution of O_2 and CO_2 in the blood and the body exert a major influence on the level of ventilation; the changes in level of ventilation, in turn, alter the amount and distribution of CO_2 and O_2. Because of this interplay, the amount of O_2 and CO_2 in the body and its distribution can be considered as the controlled plant of the respiratory control system and, as such, is an important component of mathematical models which attempt to simulate ventilatory changes.

In this study a mathematical model of the controlled plant is presented which describes the effect of changes in ventilation on blood and tissue O_2 and CO_2 tensions. The present model differs from others in that O_2 and CO_2 tensions and con-

centrations are considered to vary continuously not only with time but also spatially in the tissues and the blood; therefore, the controlled plant is described by a set of partial differential equations.

In previous mathematical models, either of the entire respiratory system or of the controlled plant per se, the body is lumped into one or more compartments and described by a set of ordinary differential equations (Cherniack et al., 1966, 1968; Defares et al., 1960; Farhi and Rahn, 1960; Fowle and Campbell, 1964; Grodins et al., 1954, 1967; Horgan and Lange, 1965; Longobardo et al., 1966, 1967; Matthews et al., 1968; Milhorn et al., 1965; Staw, 1968; Tenney and Lamb, 1964). For example, in Grodins' classic model of the respiratory system (Grodins et al., 1954), the total body CO_2 is treated as though it were confined to a single venous compartment and the functional residual capacity of the lung. In the Farhi and Rahn (1960) model of CO_2 stores, the total body CO_2 is assumed to be stored in multiple compartments connected in parallel via the blood circulation. Their multicompartment model has proved to be quite accurate in describing the long-term effects of a change in ventilation on the stored CO_2; however, the measurements in humans and dogs during the first few minutes of either apnea or hyperventilation showed that the rate of change of CO_2 tension is greater than that predicted by the Farhi and Rahn model (Cherniack et al., 1966; Fowle and Campbell, 1964).

Longobardo et al. (1967) modified the Farhi and Rahn model in order to improve the accuracy of its predictions. Their study showed that for the first few minutes of hyperventilation or apnea the predicted time change of CO_2 tension is only slightly improved by increasing the number of compartments. Moreover, their results indicated that the entire storage capacity of the body for CO_2 must be low immediately after a change in ventilation. They suggested that this low storage capacity might be caused by slow chemical reactions involved in the buffering of CO_2 by cells.

In the six-compartment model of Matthews et al. (1968), the subdivision of tissue compartments into extracellular and intracellular spaces and the introduction of a diffusion barrier for bicarbonate between the two spaces is a conceptual improvement over earlier models in which extracellular space, intracellular space, and capillary blood were lumped together in each tissue compartment. In their model, since extracellular and intracellular CO_2 tensions are identical with and equal to those in the venous blood leaving the tissue compartment, the flow of physically dissolved CO_2 between its site of metabolic production and the capillary blood is still assumed to be unrestricted.

In Staw's (1968) model of CO_2 stores, each tissue compartment is subdivided into an extracellular space and an intracellular space by a cellular membrane which acts as a diffusion barrier for each of the chemical species involved; tissue storage capacity for CO_2 is assumed to be about one-half that of blood. Although his model is not capable of reproducing the rapid changes in CO_2 tension observed during the first minute of either apnea or hyperventilation in dogs (Cherniack et al., 1966), it does reproduce the experimental results for the second to sixth minutes reasonably well.

Staw attributed this satisfactory reproduction by his model of experimental changes measured by Cherniack to the resistance of the cellular membrane to the diffusion of physically dissolved CO_2.

Thus, lumped parameter models described by ordinary differential equations have been successful to varying degrees in simulating the slowly varying dynamic behavior of the respiratory plant, but their major deficiency is an inability to predict accurately the fast response during short time transients that have been observed experimentally. One reason for this deficiency may be that lumping parameters to obtain ordinary differential equations gives rise to models with time constants that are too large. Also, in order to obtain the ordinary differential equations, it has been assumed that O_2 and CO_2 tensions in each compartment are uniform and equal to those existing in the venous blood. This assumption is not supported by experimental evidence (Coburn and Mayers, 1968; Whalen and Nair, 1967) which indicates that tissue partial pressures may differ considerably from those measured in the venous blood. A further theoretical disadvantage of lumped parameter models is that only average values of the variables for each compartment are obtained. Chemoreceptors may sense chemical conditions at specific locales which, after a disturbance, may change in a different way than the average conditions calculated from the lumped models.

These observations suggest that a lumped parameter model may be inadequate and that the spatial variations of the variables should be considered in describing the transient behavior of the system. In the model described in this paper, O_2 and CO_2 concentrations and tensions are considered as distributed in time and in one spatial coordinate throughout the body. With respect to tissue parameters, the body tissue is divided into three separate groups. Existing nonlinear algebraic equations for the O_2 and CO_2 dissociation curves, including the Haldane and Bohr effects for blood, are employed to relate concentrations and partial pressures. Time-variable delays in arterial and venous transport of the respiratory gases are included. The system of nonlinear equations describing the controlled plant of the respiratory system is numerically integrated. Experimental studies were conducted in order to test the validity of the model and to obtain realistic estimates for the values of unknown parameters.

THEORY

General Description of the Model

The proposed distributed parameter model is still an idealized model but it is more realistic than the lumped parameter approach of earlier models. Let $\mathbf{u}(x, t) = [P(x, t), P'(x, t), \mathrm{pH}(x, t)]$ denote the three-dimensional vector where P and P' are the oxygen and carbon dioxide tensions, respectively, x is the spatial coordinate, and t is time. In the controlled plant, the rate of ventilation $\dot{V}(t)$ is the input and the distribution $\mathbf{u}(x, t)$ is the output. In the closed loop respiratory regulator, $\dot{V}(t)$

is related to $\mathbf{u}(x, t)$ by a functional relationship which includes the chemoreceptors and the respiratory center (the controller). This functional relationship is not studied in this paper.

The vascular system which forms a loop in which the blood is recycled is divided into four subsystems as shown in Fig. 1. The first subsystem consists of the systemic capillary bed and the body tissue. Blood enters this subsystem at the precapillary conditions $\mathbf{u}(0, t)$ and leaves it at the mixed postcapillary venous conditions $\mathbf{u}(1, t)$. The second subsystem consists of the pulmonary capillary bed and the functional residual capacity of the lungs with the rate of ventilation $\dot{V}(t)$ as the input; blood enters this subsystem at the venous conditions $\mathbf{u}_v(t)$ and leaves it at the arterial conditions $\mathbf{u}_a(t)$. The third subsystem, referred to as "venous time delay," relates the venous blood conditions $\mathbf{u}_v(t)$ entering the lung to the mixed postcapillary venous blood conditions $\mathbf{u}(1, t)$. The fourth subsystem, referred to as "arterial time delay,"

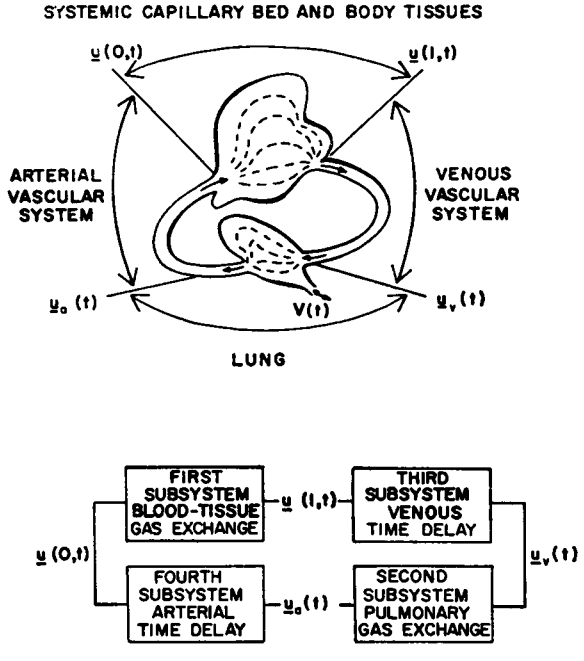

FIGURE 1

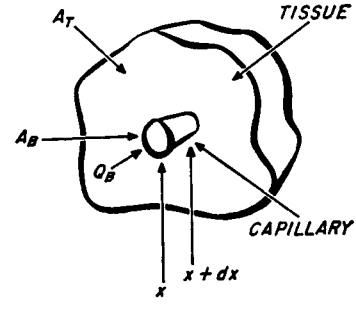

FIGURE 2

FIGURE 1 Schematic and block diagram of the controlled plant of the respiratory system, consisting of the arterial and venous vascular systems, the systemic and pulmonary capillary beds (capillaries are indicated by broken lines), the body tissues, and the functional residual capacity of the lung. $\dot{V}(t)$ is ventilation and $\mathbf{u}$ represents a three-dimensional vector with components P_{O_2}, P_{CO_2}, and pH. The controlled plant is divided into four subsystems as shown in the block diagram representation.

FIGURE 2 Cross-section through a typical capillary surrounded by systemic tissue. x denotes the location of the cross-section with respect to the capillary length, A_T is the cross-sectional area of the tissue supplied by the capillary, A_B is the cross-sectional area of the capillary, and Q_B is its blood flow rate.

relates the precapillary blood conditions $\mathbf{u}(0, t)$ to the arterial blood conditions $\mathbf{u}_a(t)$ leaving the lung. Each of the subsystems will be modeled separately in the following sections.

First Subsystem: Blood-Tissue Gas Exchange

Because this subsystem plays a major role in determining the dynamic response of the system and in deriving the model, great emphasis is laid on it and experiments were performed to test the accuracy of the model of this subsection before the entire model of the controlled plant was constructed and tested. While the blood flows through the capillaries, exchange of O_2 and CO_2 with the surrounding tissue occurs and the chemical composition of the blood changes continuously along the capillary. The blood leaving the capillaries is then mixed and leaves the subsystem as mixed venous blood.

The Governing Equations

Fig. 2 shows a cross-section through a typical capillary surrounded by tissue. Let A_B and A_T denote the cross-sectional areas of the capillary and of the tissue being supplied by the capillary, respectively, and x denote the length of the capillary between the arterial end and the cross-section. It is now assumed that variations of concentrations and partial pressures in blood and tissue are small in the radial direction, that the blood-tissue interface constitutes a diffusion barrier for O_2 and CO_2, and that the diffusion of O_2 and CO_2 across the blood-tissue interface is proportional to the respective tension difference between blood and tissue.

Let $C_B(x, t)$ and $C_T(x, t)$ be the concentrations of oxygen at location x at time t in blood and tissue, respectively, and $P_B(x, t)$ and $P_T(x, t)$ their corresponding partial pressures. The conservation of oxygen expressed per unit volume of blood (equation 1) and per unit volume of tissue (equation 2) can be expressed as

$$\frac{\partial C_B(x, t)}{\partial t} + v(t) \frac{\partial C_B(x, t)}{\partial x} = D_B \frac{\partial^2 C_B(x, t)}{\partial x^2} + k[P_T(x, t) - P_B(x, t)], \quad (1)$$

$$\frac{\partial C_T(x, t)}{\partial t} = D_T \frac{\partial^2 C_T(x, t)}{\partial x^2} + \frac{A_B}{A_T} k[P_B(x, t) - P_T(x, t)] - M(x, t), \quad (2)$$

where D_B and D_T are oxygen diffusion coefficients for blood and tissue, respectively, k is a mass transfer coefficient per unit blood volume, $M(x, t)$ denotes the amount of metabolically consumed oxygen per unit time and unit volume of tissue, and $v(t)$ is the blood velocity. It is assumed that D_B, D_T, and k are constants, that $v(t)$ varies with t (time) only and not with x (the position along the capillary), and that $M(x, t)$ varies with both x and t. Equation 1 states that the rate of change of O_2 concentration in blood is determined by axial convection resulting from the flow of blood and by axial and radial diffusion due to gradients of O_2 tension. Equation 2 may be similarly interpreted.

Bailey (1967) has shown theoretically that, under steady-state conditions, the inclusion of axial diffusion in models has little influence on the oxygen distribution in tissue and blood despite extremely high axial tension gradients for O_2 in blood and tissue resulting from the bend of the oxygen-hemoglobin dissociation curve at high saturation. It seems probable that the axial diffusion in tissue and blood is also negligible under dynamic conditions, and axial diffusion of O_2 and CO_2 is therefore not included in the model. In equation 2 the parameter A_B/A_T may be expressed as A_BL/A_TL, i.e. as the ratio of capillary blood volume to the volume of tissue, where L is the length of the capillary. The expression A_BL/A_TL may be regarded as a capacitance ratio and is denoted by V_R. In equations 1 and 2, x may be considered as normalized such that $0 \leq x \leq 1$ if the coefficients $v(t)$, D_B, and D_T are replaced by $v(t)/L$, D_B/L^2, and D_T/L^2, respectively; however, the axial diffusion terms are neglected and the parameter $v(t)/L$ is expressed as

$$\frac{v(t)}{L} = \frac{A_B\, v(t)}{A_B\, L} = \frac{Q_B(t)}{(A_T\, L)V_R},$$

where $Q_B(t)/A_TL$ is the rate of blood flow per unit volume of tissue, is called the blood perfusion rate of tissue, and is denoted by P_R. Assuming that the axial diffusion terms are negligible and considering x as a normalized coordinate, equations 1 and 2 become

$$\frac{\partial C_B(x, t)}{\partial t} + \frac{P_R(t)}{V_R}\frac{\partial C_B(x, t)}{\partial x} = k[P_T(x, t) - P_B(x, t)], \qquad (3)$$

$$\frac{\partial C_T(x, t)}{\partial t} = V_R\, k[P_B(x, t) - P_T(x, t)] - M(x, t), \qquad 0 \leq x \leq 1, t > 0. \qquad (4)$$

It should be noted that x now is normalized length and therefore is dimensionless. The dimensions of each term in equations 3 and 4 are thus concentration over time.

The two equations expressing the conservation of CO_2 in blood and tissue are similar to equations 3 and 4, except that $-M(x, t)$ in equation 4 is replaced by $R_QM(x, t)$ where R_Q is the respiratory quotient, i.e., the ratio of metabolically produced CO_2 to the metabolically consumed O_2. Letting C', P', and k' represent the concentration, partial pressure, and mass transfer coefficient, respectively, of CO_2, the equations of conservation of CO_2 per unit volume of blood (equation 5) and per unit volume of tissue (equation 6) are given by

$$\frac{\partial C'_B(x, t)}{\partial t} + \frac{P_R(t)}{V_R}\frac{\partial C'_B(x, t)}{\partial x} = k'[P'_T(x, t) - P'_B(x, t)], \qquad (5)$$

$$\frac{\partial C'_T(x, t)}{\partial t} = V_R\, k'[P'_B(x, t) - P'_T(x, t)] + R_Q\, M(x, t), \qquad 0 \leq x < 1, t > 0 \qquad (6)$$

If there are n capillaries and $C_{Bi}(1, t)$ is the oxygen concentration of blood leaving the ith capillary and $Q_i(t)$ is its blood flow rate, then $C_B(1, t)$, the oxygen concentration of the mixed venous postcapillary blood, is given by

$$C_B(1, t) = \frac{\sum_{i=1}^{n} Q_i(t) C_{Bi}(1, t)}{\sum_{i=1}^{n} Q_i(t)}. \tag{7}$$

Similarly, $C'_B(1, t)$, the carbon dioxide concentration of mixed venous postcapillary blood, is given by

$$C'_B(1, t) = \frac{\sum_{i=1}^{n} Q_i(t) C'_{Bi}(1, t)}{\sum_{i=1}^{n} Q_i(t)}. \tag{8}$$

Relationships between Concentrations and Partial Pressures

It is noted that equations 3–6 are expressed in terms of both concentrations and partial pressures. It is therefore necessary to express concentrations in terms of partial pressures and vice versa. These relationships are now discussed.

Relationship between Oxygen Partial Pressure and Concentration in Blood. In blood, oxygen is present in two forms, namely, physically dissolved and chemically bound to hemoglobin according to the equation

$$\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO_2}.$$

This chemical reaction is very fast. The half-time of the forward reaction is about 0.071 sec, and that of the backward reaction, 0.038 sec (Roughton, 1964). In this study, the reaction is assumed to be instantaneous; however, P_B is related nonlinearly to C_B, to the hemoglobin capacity of blood $C_{B\,\max}$, and to pH (Bohr effect). The oxygen dissociation curve of Gomez (1960) is believed to be the most accurate one and is employed in this study. It may be stated as

$$\begin{aligned} C_B &= C_{B\,\max}\, w/(1 + w), \\ w &= 0.925z + 2.8z^2 + 30.0z^3, \\ z &= \{0.005727 \exp [(\mathrm{pH} - 7.4)\ 1.812] + 0.004273\} P_B, \end{aligned} \tag{9}$$

where C_B and $C_{B\,\max}$ are in milliliters per cubic centimeter and P_B is in millimeters Hg. Fig. 3 shows the hemoglobin saturation in per cent, i.e., $100\ C_B/C_{B\,\max}$ vs. P_B for different values of pH as obtained from equations 9. It follows that

$$P_B = g(C_B, \mathrm{pH}, C_{B\,\max}), \tag{10}$$

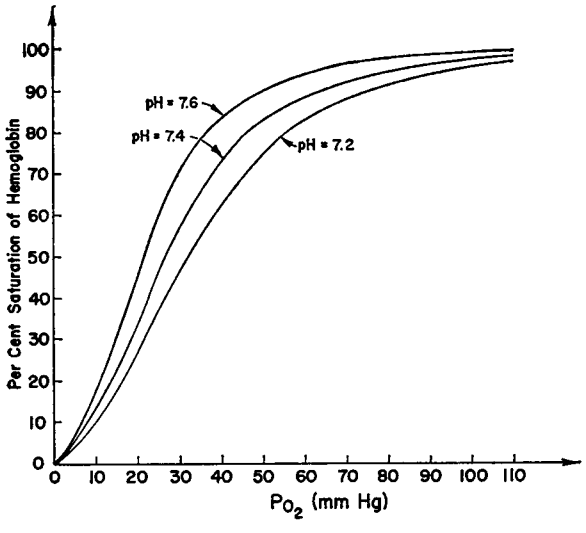

FIGURE 3

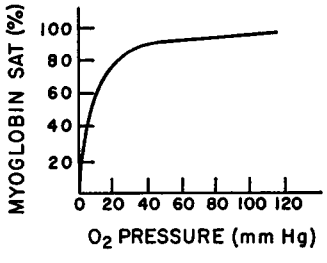

FIGURE 4

FIGURE 3 Graphical representation of the O_2 dissociation curve of blood showing the effect of pH. Curves are shown for constant pH and were computed as follows: per cent saturation of hemoglobin $= 100\, w/(1 + w)$, where $w = 0.925\, z + 2.8\, z^3 + 30.0\, z^8$ with $z = \{5.727 \times 10^{-8} \exp [(\text{pH} - 7.4)\ 1.812] + 4.273 \times 10^{-8}\}\ P_{O_2}$.

FIGURE 4 Oxygen dissociation curve of myoglobin from Roughton (1964). The curve shows the per cent saturation of myoglobin vs. the oxygen partial pressure in millimeters Hg.

where g is the inverse relationship which can be obtained from the dissociation equation 9.

Relationship between Oxygen Partial Pressure and Concentration in Tissue. In tissues which do not contain myoglobin, only physically dissolved oxygen is present and we have the relationship

$$C_T = aP_T, \tag{11}$$

where a is the oxygen solubility of tissue. In tissues containing myoglobin, e.g. muscle tissue, oxygen is present in two forms, namely, physically dissolved and chemically bound to myoglobin. The oxygen dissociation in muscle tissue then has the form

$$C_T = aP_T + f(P_T, C_{T\,\max}), \tag{12}$$

where the first term on the right-hand side expresses the physically dissolved oxygen and the second term the chemically bound oxygen, and $C_{T\,\max}$ is the myoglobin capacity of the tissue. The experimentally obtained relationship f given by Roughton (1964) is shown in Fig. 4. In this study, the nonlinear curve is approximated by piece-

wise linear relationships as

$$f(P_T, C_{T\,max}) = 0.0825\ P_T C_{T\,max}, \qquad P_T \leq 8;$$
$$= [0.66 + (P_T - 8)\ 0.0072]\ C_{T\,max}, \qquad 8 < P_T \leq 41;$$
$$= [0.9 + (P_T - 4)\ 0.000678]\ C_{T\,max}, \qquad P_T > 41. \tag{13}$$

It can be seen from Fig. 4 that these equations closely approximate the O_2 saturation curve within the range of physiological interest.

Relationship between Carbon Dioxide Partial Pressure and Concentration in Blood and Tissue. Carbon dioxide in blood and tissue is mainly present as physically dissolved CO_2 and as bicarbonate (HCO_3^-). The relationship between dissolved CO_2 and bicarbonate is governed by the reactions.

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-,$$

$$H^+ + B^- \rightleftarrows HB,$$

where B^- denotes the buffer ions. The second stage of the first reaction as well as the second reaction are practically instantaneous, whereas the first stage of the first reaction depends upon the availability of appropriate enzymes, e.g., carbonic anhydrase.

In tissue containing little carbonic anhydrase, e.g. muscle, the hydration of CO_2 is a slow process (Maren, 1967). In simulating the short-term experiments of this study, the CO_2 hydration in these tissues is neglected; i.e. the amount of bicarbonate produced by CO_2 hydration during this time period is assumed to be negligibly small and hence

$$dC'_T/dt = a'\ dP'/dt, \tag{14}$$

where C'_T is in milliliters per cubic centimeter, P'_T is in millimeters Hg, and a' is the carbon dioxide solubility of tissue.

In capillary blood and in tissues such as brain where carbonic anhydrase is present in sufficiently great concentration, the CO_2 hydration process is very fast and buffering by noncarbonate buffers is practically instantaneous. Blood and these tissues, therefore, may be assumed to be internally in chemical equilibrium.

For blood the following relationship between CO_2 concentration and partial pressure is employed in this study (Cherniack et al., 1968):

$$C'_B = (0.149 - 0.014S)P'^{(0.35)}_B + (HCO_3^- \text{ correction term}), \tag{15}$$

where C'_B is in milliliters per cubic centimeter, P'_B is in milliliters Hg, and S is the HbO_2 saturation (%/100). The HCO_3^- correction term has been added in this equa-

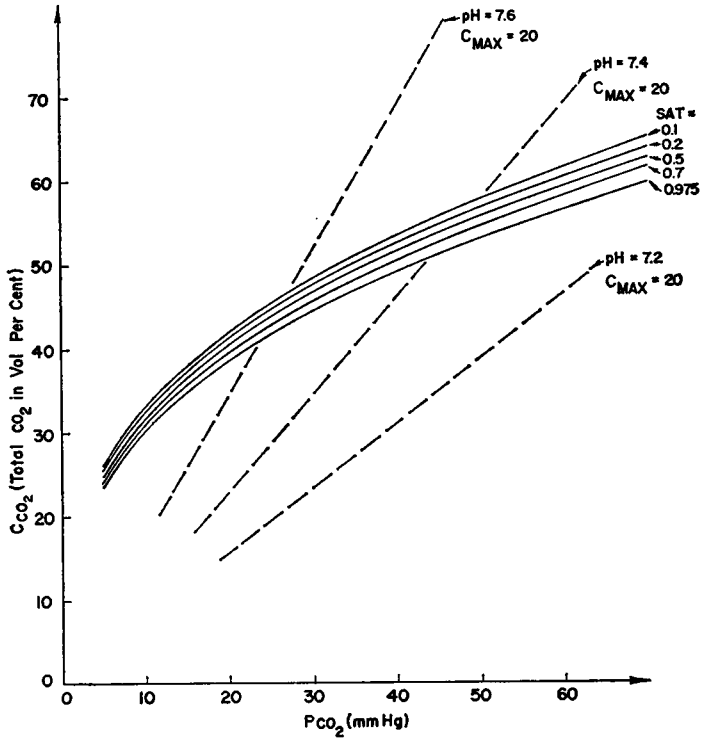

FIGURE 5 Graphical representation of the blood CO_2 dissociation equation $C_{CO_2} = (14.9 - 1.4\ SAT)\ P_{CO_2}^{0.35}$. Curves are shown for different oxygen saturations (SAT). Broken lines indicate constant pH at a hemoglobin concentration of 20 ml/100 ml.

tion to compensate for variations in standard bicarbonate in individual experiments. Fig. 5 gives a plot of equation 15 without the correction term. It can be seen that the Haldane effect, i.e. the dependence on oxygenation, is included.

The pH may be obtained from the Henderson-Hasselbach equation

$$\mathrm{pH} = \mathrm{pK} + \log\,[(C'_p - a'P'_B)/(a'P'_B)], \tag{16}$$

where pK is the dissociation constant and C'_p is the total CO_2 concentration of plasma. The relationship between whole blood and plasma CO_2 concentrations is dependent on the pH and on the hemoglobin capacity of the blood. The pH dependence, however, is small and is neglected, and the relationship employed is given by

$$C'_p = [1.19 + (C_{B\,\max} - 0.2)]C'_B\,, \tag{17}$$

where $C_{B\,\max}$ is the hemoglobin capacity of blood in milliliters per cubic centimeter.

It can be seen that equations 3, 4, and 5, 6 are coupled because of the Bohr and

Haldane effects via the O_2 and CO_2 dissociation curves of blood. This subsystem is then described by a set of coupled equations, namely, the four first-order partial differential equations 3–6, and the algebraic equations relating concentrations and partial pressures of O_2 and CO_2 in blood and tissue and the relationship for pH. Nonlinearities are introduced by the nonlinear dissociation curves.

In addition to the relationships between concentrations and partial pressures, equations 3–6 have introduced six parameters, namely, V_R, P_R, k, k', M, and R_Q. The equations have been derived for a single capillary. Although it is to be expected that the parameters involved do vary from capillary to capillary, at best, average values for these parameters in specific tissues can be measured experimentally and were therefore used in the model (Barcroft and Kato, 1949; Drabkin, 1951; Gibson et al., 1946; Green, 1944; Kety, 1951; Krogh, 1919; Otis, 1963; Pappenheimer, 1953; Spector, 1956; Stainsby and Otis, 1964).

Second Subsystem: Pulmonary Gas Exchange

This subsystem consists of the pulmonary capillary bed and the functional residual capacity of the lung. As shown in Fig. 1, blood enters the subsystem under the venous conditions $\mathbf{u}_v$ and leaves it under the arterial conditions $\mathbf{u}_a$. Because of the large surface area available for gas diffusion in the lungs, it seems likely that most of the pulmonary capillary blood is in equilibrium with the alveolar gas with respect to O_2 and CO_2 tensions (Flumerfelt and Crandall, 1968). A lumped parameter model, therefore, seems adequate to describe the dynamics of this subsystem accurately and it is employed in this study. Therefore, oxygen and carbon dioxide tensions are assumed to be uniform throughout the blood in the pulmonary capillary bed and equal to those in the functional residual capacity. The following assumptions were also made:

(*a*) Oxygen and carbon dioxide concentrations and partial pressures are uniform throughout the functional residual capacity of the lung; and

(*b*) The periodicity of ventilation can be neglected.

The amount of oxygen stored in the subsystem at time t is

$$V_B C_a(t) + V_F C_F(t),$$

where V_B and V_F, which are assumed to be constant, are the volume of blood in the pulmonary capillary bed and the volume of the functional residual capacity, respectively, and C_a and C_F are concentrations of O_2 in arterial blood leaving the lung and in the functional capacity, respectively. The net rate of oxygen gain due to ventilation is given by

$$\dot{V}(t)[C_M(t) - C_F(t)],$$

where C_M denotes the concentration of O_2 in the breathing mixture and $\dot{V}(t)$ is the

rate of ventilation (volume/time). The net rate of oxygen gain due to blood is given by

$$Q_B(t)[C_v(t) - C_a(t)],$$

where Q_B is the blood flow rate and C_v is the O_2 concentration in venous blood entering the lung. The equation for the conservation of O_2 in the subsystem then can be expressed as

$$\frac{d}{dt}[V_B C_a(t) + V_F C_F(t)] = \dot{V}(t)[C_M(t) - C_F(t)] + Q_B(t)[C_v(t) - C_a(t)]. \quad (18)$$

In the functional residual capacity of the lungs, O_2 and CO_2 are present in a gaseous phase and the relationship between concentration and partial pressure for O_2 is given by

$$C_F = P_F/(P_{bar} - 47), \quad (19)$$

where C_F is in milliliters per cubic centimeter, P_F is in millimeters Hg, P_{bar} is the barometric pressure in millimeters Hg, and the number 47 represents the pressure of water vapor in the functional residual capacity. For CO_2 in the functional residual capacity, equation 19 holds with C_F and P_F being replaced by C_F' and P_F', respectively. Noting that according to assumption 19 $P_a = P_F$, and employing equation (19), equation 18 can be expressed as

$$\frac{dP_a}{dt} = \frac{V(P_M - P_a)/(P_{bar} - 47) + Q_B(C_v - C_a)}{V_B(dC_a/dP_a) + V_F/(P_{bar} - 47)}. \quad (20)$$

Similarly, the conservation equation for CO_2 is expressed by

$$\frac{dP_a'}{dt} = \frac{V(P_M' - P_a')/(P_{bar} - 47) + Q_B(C_v' - C_a')}{V_B(dC_a'/dP_a') + V_F/(P_{bar} - 47)}. \quad (21)$$

In equation 20, the relationship between C_a and P_a is given by the O_2 dissociation curve of blood given by equations 9, 16, and 17. In equation 21, the relationship between C_a' and P_a' is given by the CO_2 dissociation curve of blood given by equations 15–17. It is noted therefore that equations 20 and 21 are nonlinear and coupled because of the Bohr and Haldane effects.

Third and Fourth Subsystems: Arterial and Venous Time Delays

The arterial and venous subsystems are modeled on the assumptions that blood is incompressible and that diffusion of O_2 and CO_2 in the direction of flow are negligible. Under these assumptions, the arterial and venous subsystems can be represented

as pure lags in transportation. The arterial relationship is given by

$$\mathbf{u}(0, t) = \mathbf{u}_a[t - T_a(t)]. \tag{22}$$

If the blood flow rate Q_B is constant, then T_a is the arterial residence time given by $T_a = V_A/Q_B$ where V_A is the arterial blood volume. For variable blood flow, T_a is time dependent and is obtained from the relationship

$$\int_{t-T_a(t)}^{t} Q_B(t)\, dt = V_A. \tag{23}$$

Similarly, the venous relationship is given by

$$\mathbf{u}_v(t) = \mathbf{u}(1)[\, t - T_v(t)], \tag{24}$$

where the time-varying venous transportation lag $T_v(t)$ is obtained from

$$\int_{t-T_v(t)}^{t} Q_B(t)\, dt = V_v, \tag{25}$$

where V_v is the venous blood volume.

METHODS

Experimental Methods

Experimental studies were conducted to test the validity of the first subsystem of the model, to estimate parameter values, and to test the complete model of the controlled plant. To test the first subsystem, blood-muscle tissue gas exchange was investigated while blood-tissue gas exchange for the whole body was studied to verify the validity of the complete model.

The effects of two different ventilatory disturbances were studied; namely, asphyxia and apneic oxygenation. The apneic oxygenation experiments allowed changes in CO_2 storage to be evaluated while arterial blood and saturation and presumably arterial O_2 stores were kept constant. Not only did the asphyxia experiment produce alterations in CO_2 storage but it also produced rapid changes in tissue and blood O_2 stores which are desirable for the study of the dynamic behavior of these stores.

The experiments were performed on dogs weighing 13–16.2 kg. The animals were anesthetized with pentobarbital (25–30 mg/kg) and paralyzed with succinylcholine (1–2 ml).

Blood-Muscle Tissue Gas Exchange. Muscle was chosen for the set of experiments because it constitutes 40% of the total body mass (dogs 1–3). Arterial blood flow into the leg was recorded continuously using a gated sine wave electromagnetic flow meter (Biotronex Lab, Inc., Silver Spring, Md.) placed around the femoral artery. In order to measure only the blood flow to the muscles, the hind limb was skinned and vessels supplying the hind limb other than the femoral artery were ligated. Steady-state conditions were obtained during a control period of constant artificial ventilation of at least 20 min with ambient air. Artificial ventilation then was stopped, and samples of arterial and venous blood were taken from the hind limb during the control period of artificial ventilation and at 30–60 sec intervals during asphyxia; arterial blood flow was continuously measured during both the control and test

periods. The blood samples were measured for O_2 and CO_2 partial pressures, concentrations, pH, and hematocrits. After 3 min of asphyxia, artificial ventilation was resumed, but using 100% O_2 instead of air, until steady-state conditions again were obtained. Breathing was then stopped but arterial O_2 saturation was kept constant by connecting the animal via his endotracheal tube to a spirometer containing 100% O_2 (apneic oxygenation). Blood samples were taken during the control period of artificial ventilation and after ½, 1, 2, 3, 4, and 6 min of apneic oxygenation. Circulation time across the leg was measured using indocyanine green and a densitometer (Gilford Instrument Labs, Inc., Oberlin, Ohio). The dye was injected into the femoral artery by means of a catheter placed so that its tip was just below the inguinal ligament while sampling was performed through the femoral vein. At the conclusion of the experiment, the muscles of the hind limb were weighed.

Blood-Tissue Gas Exchange in the Whole Body. In this study asphyxia experiments were performed as described above except that flow through the pulmonary artery rather than through the femoral artery was continuously measured using a gated sine wave flow probe (dogs 4 and 5). Circulation time from lung to systemic artery and cardiac output in the steady state were obtained by standard dye dilution techniques using indocyanine green (Hamilton et al., 1948).

O_2 tension was measured using a Clark electrode, CO_2 tension using a Severinghaus electrode, and pH using a glass electrode (Radiometer, London Co., Cleveland, Ohio). In each sample O_2 and CO_2 concentrations were also measured by the technique of Van Slyke and Neil. Hematocrit was determined by a micromethod.

Methods of Computation

A closed form solution of equations 3–6 along with the dissociation relationships is not possible because of the complicated nature of the nonlinearities. The equations were therefore numerically integrated on an IBM 360 digital computer. The grid size that proved satisfactory was such that

$$\Delta t < (V_R/P_R)\Delta x,$$

where Δt and Δx are step sizes in time and normalized spatial coordinate, respectively. The initial conditions were obtained from the steady-state distribution prevailing when a disturbance is introduced. For steady state from equations 3–6, we get

$$\frac{d}{dx} C_B(x) = -\frac{M(s)}{P_R}, \tag{26}$$

$$P_T(x) = P_B(x) - \frac{M(s)}{V_R k}, \tag{27}$$

$$\frac{d}{dx} C'_B(x) = \frac{R_Q M(s)}{P_R}, \tag{28}$$

$$P'_T(x) = P'_B(x) + \frac{R_Q M(s)}{k' V_R}. \tag{29}$$

Equations 26–29 combined with the dissociation equations were solved to obtain the initial distribution after evaluating the parameters that are involved.

RESULTS

The Blood-Muscle Gas Exchange

The $C_{B\,max}$ of equation 9 was computed from the steady-state values of P_B, C_B, and pH of arterial blood determined experimentally. The O_2 saturation of hemoglobin was obtained from equation 9 and hence $C_{B\,max}$ could be calculated. The myoglobin content of muscle tissue was taken to be 1.64×10^{-3} ml/ml (Drabkin, 1951). For muscle tissue, in equation 14 we used $a' = 7.0 \times 10^{-4}$ ml/ml per mm Hg which is the solubility of CO_2 in water. The HCO_3^- correction term of equation 15 was obtained by first computing uncorrected C'_B and then subtracting this value from the experimentally obtained steady-state C'_B. Although tissue volume is not a direct parameter of the subsystem, it was employed for normalizing parameter values. The weight of the muscle was measured and muscle volume was obtained by assuming that all of the muscle is water and that the specific gravity of the muscle tissue is unity. The weights of the hind limb muscles were 689 g, 750 g, and 1045 g for dogs 1, 2, and 3, respectively. It was assumed that under steady-state conditions, the metabolic activity is uniform throughout the muscle of the hind limb. By dividing the total O_2 consumption by the tissue volume, the initial (steady-state) value M_S was obtained. The values of M_S thus obtained in ml/(ml·sec) 10^{-5} were 1.278, 0.8, and 2.48 for dogs 1, 2, and 3. Since the studies of Stainsby and Otis (1964), Otis (1963), and Cherniack et al. (1968) suggest that the metabolic activity of muscle decreases during asphyxia, in the present study local oxygen consumption under dynamic conditions was expressed as

$$M(x, t) = X(x)T(t), \tag{30}$$

where $X(x)$ expresses the local availability of O_2 and may vary between 1 and 0, and $T(t)$ represents the experimentally observed (Cherniack et al., 1968; Otis, 1963) decrease in metabolic activity due to low O_2 tension $P_a(t)$ in arterial blood. It was assumed that

$$\begin{aligned} T(t) &= M_S, && P_a(t) \geq 45 \text{ mm Hg}; \\ &= M_S P_a(t)/45, && P_a(t) < 45 \text{ mm Hg}. \end{aligned} \tag{31}$$

The respiratory quotient was obtained by dividing the initial total CO_2 production by the initial total O_2 consumption. Values of R_Q used for the three dogs were 1.00, 0.70, and 0.96 for the asphyxia experiments, and 0.89, 1.00, and 0.95 for the diffusion respiration experiments. The CO_2 production was obtained by multiplying the initial arterial-venous CO_2 concentration difference by the blood flow rate. The value of the blood perfusion rate of tissue $P_R(t)$ was obtained by dividing the continuously recorded time-variable blood flow rate by the constant tissue volume. It was necessary to estimate the value of V_R, i.e. the ratio of capillary blood to tissue

volume, since the number of open capillaries in muscle tissues at rest varies between 40 and 270/mm² (Barcroft and Kato, 1919; Krogh, 1919; Stainsby and Otis, 1964; Tenney and Lamb, 1964). Assuming that all capillaries are parallel and have a diameter of 7.2 μ, the value of V_R is between 0.0017 and 0.011. The mass transfer coefficients k and k' of O_2 respectively, were obtained from the steady-state equations 27 and 29 by assuming values for the steady-state tension difference between blood and tissue and employing the values of the other parameters in those equations.

Since the values of the parameters V_R , k, and k', are uncertain and were not determined, it seemed desirable to investigate the effect of variations in these parameters on the computed O_2 and CO_2 tensions in venous blood and to compare these computed values with those obtained experimentally. Fig. 6 shows the results obtained for O_2 tensions in dog 1 when V_R was varied from 0.001 to 0.008 while k was maintained at a constant value of 4.66×10^{-4} ml O_2/ml blood per sec per mm Hg; Fig. 7 shows the results obtained when k was varied between 1.165×10^{-4} and

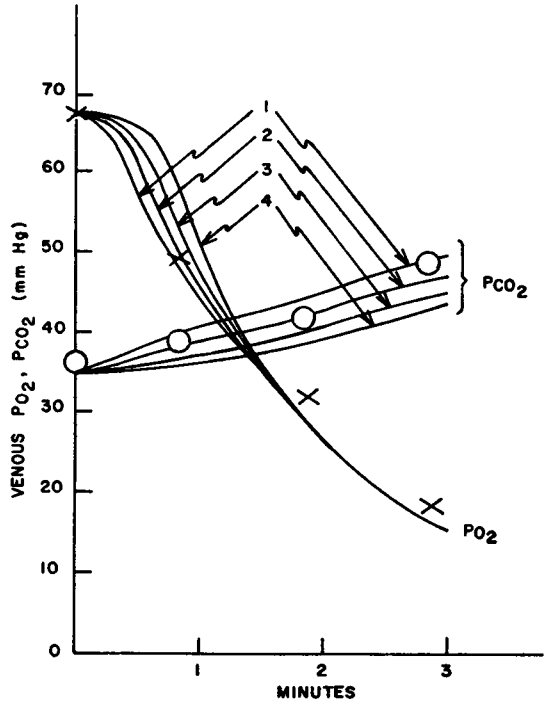

FIGURE 6 The effect of the blood-to-tissue volume ratio V_R on the computed muscle venous P_{O_2} and P_{CO_2} during asphyxia in dog 1. The mass transfer coefficients k and k' are kept constant at 4.66×10^{-4} and $5.5 \times 4.66 \times 10^{-4}$ ml/ml of blood per mm Hg per sec respectively, whereas V_R is equal to 0.001 (1), 0.002 (2), 0.004 (3), and 0.008 (4). Measured muscle venous P_{O_2} (×) and P_{CO_2} (○) are shown for comparison.

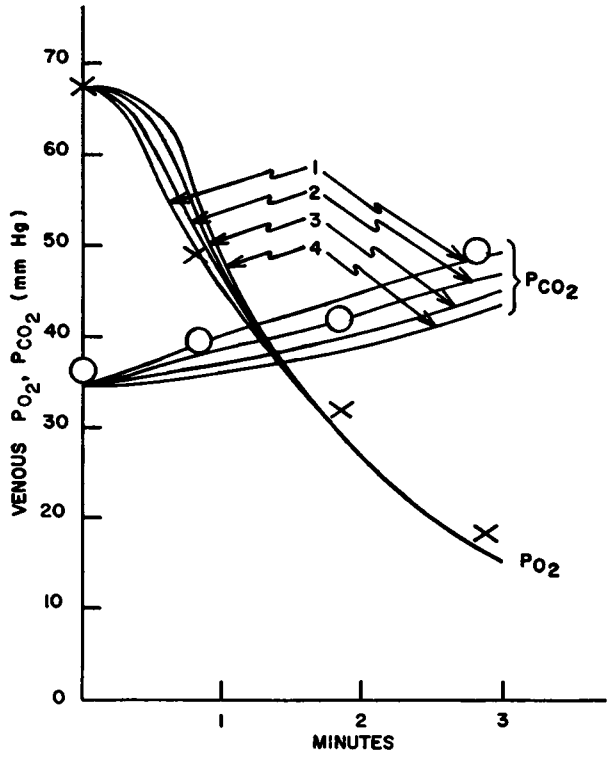

FIGURE 7 The effect of the O_2 and CO_2 mass transfer coefficients k and k' on the computed muscle venous P_{O_2} and P_{CO_2} during asphyxia in dog 1. k in ml O_2/ml of blood per mm Hg per sec is 1.165×10^{-4} (1), 2.33×10^{-4} (2), 4.66×10^{-4} (3), and 9.32×10^{-4} (4), with k' equal to 5.5 k; V_R is kept constant at 0.004. Measured muscle venous P_{O_2} (×) and P_{CO_2} (○) are shown for comparison.

9.32×10^{-4} with k' equal to 5.5 k while V_R was kept at a constant value of 0.004.[1] A comparison of Figs. 6 and 7 shows that it is the product of $V_R k$ and not the separate value of V_R or k which is important in determining the results; and it is also apparent that the best results are obtained when the product of $V_R k$ is approximately 7×10^{-7} which would correspond to a gradient in the steady state of approximately 20 mm Hg between capillary and tissue O_2 tensions. Figs. 6 and 7 also show the effect of variations of V_R and k' on computed values of muscle venous P_{CO_2} and show that best results are obtained when the product of $V_R k' = 5.5\ V_R k$. This would correspond to a gradient of approximately 3.5 mm Hg between capillary and tissue CO_2 tensions.

In Fig. 8, computations made with these parameter values are compared to experi-

[1] From experiments in which indocyanine green was injected into the femoral artery and sampled in the femoral vein, the transport delay between postcapillary blood and the site of venous blood measurement was estimated to be 10 sec. Consequently venous experimental points have been shifted 10 sec backwards in time in Figs. 6 and 7.

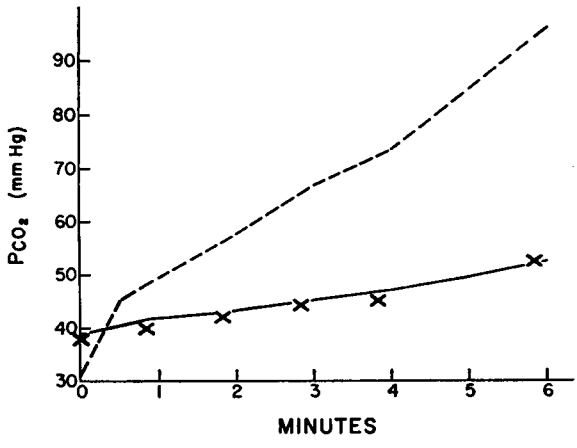

FIGURE 8 Comparison of experimental (×) and computed (solid line) muscle venous P_{CO_2} during apneic oxygenation in dog 1. The broken line indicates the measured arterial P_{CO_2} which was used as input for computation.

mental results obtained in the diffusion respiration experiment in dog 1. Both the asphyxia and diffusion respiration experimental results could be best duplicated by the same values of $V_R k$ and $V_R k'$ in dog 2; however, the experiments in dog 3 could be duplicated only when the product of $V_R k$ and $V_R k'$ was two times greater than the values used for dogs 1 and 2. Results for dogs 2 and 3 are given elsewhere (Trueb, 1970).

Dog 3 had a metabolic rate that was approximately twice that measured in dogs 1 and 2. Since considerable evidence indicates that capillary density increases in muscle with an increase in metabolic rate (Krogh, 1919; Otis, 1963; Stainsby and Otis, 1964), it is likely that the higher product of $V_R k$ and $V_R k'$ needed to simulate the experimental results obtained in dog 3 was caused by the increase in capillary density and the consequently greater V_R in dog 3 than in dogs 1 and 2 (Cater et al., 1961; Renkin et al., 1966). It is interesting that since the product of $V_R k$ and $V_R k'$ and the metabolic rate of dog 3 are all twice that of dogs 1 and 2, the gradient for O_2 and CO_2 tension in the steady state would be the same in dog 3 as in the other two animals.

The effect of myoglobin content in the muscle on the computed results was investigated by varying the value for myoglobin content between one-half and twice the originally assumed value; it was found to be negligible, undoubtedly because of the high affinity of O_2 to myoglobin which can be seen from the myoglobin dissociation curve.

Blood-Tissue Gas Exchange of the Total First Subsystem

With respect to the values for the different parameters, the total body tissue was divided into three groups, namely, muscle tissue, brain tissue, and "all other" tissue.

Muscle tissue was singled out because of its myoglobin content and low value of perfusion rate P_R. Brain tissue was considered separately because of its high, and presumably constant, metabolic rate and because of its importance as a site for respiratory chemoreceptors. Because bone and fat have low metabolism and high diffusion resistance, they play little role in short time dynamic responses, and were not included in the model.

The volumes of the three tissue groups were obtained from data obtained previously indicating that brain tissue constitutes 0.7%, muscle tissue 42%, and all other tissues 30% of the total body weight, and that the specific volume of all tissues is approximately 1 cm^3/g (Spector, 1956). The values for V_R, i.e. the capillary blood-to-tissue volume ratio, were taken as 0.05, 0.008, and 0.03 for brain tissue, muscle tissue, and all other tissues, respectively; these values correspond to capillary densities of 1170, 195, and 715 capillaries/mm^2, respectively (Barcroft and Kato, 1949; Drabkin, 1951; Gibson et al., 1946; Kety, 1951; Krogh, 1919; Tenney and Lamb, 1964). The values of the mass transfer coefficients were obtained using the assumption that the steady-state tension differences between capillary blood and tissue are about 20 mm Hg for O_2 and about 3.5 mm Hg for CO_2. This assumption is based on the results on dogs described in the previous section. This resulted in the values of k as 8.5×10^{-4}, 4.66×10^{-4}, and 7.11×10^{-4} for the brain, muscle, and all other tissues, respectively. The values of k' are 5.5 times those of k.

The metabolic rates of the tissue groups were obtained by assigning to each group a percentage of the total steady-state O_2 consumption, namely, 3% to brain tissue, 20% to muscle tissue, and 77% to all other tissues (Green, 1944; Tenney and Lamb, 1964). The respiratory quotients of brain and muscle tissue were chosen as 1.0 and 0.8 respectively (Spector, 1956) and that of the third tissue group was then computed in such a way that the over-all measured respiratory quotient of the animal was satisfied.

The blood perfusion rates of the three tissue groups were obtained as follows. The blood flow to the brain was assumed to be independent of the cardiac output but to vary with O_2 and CO_2 partial pressures in arterial blood, i.e., with $P_a(t)$ and $P_a(t)$. Grodins et al. (1967) give the following steady-state relationship

$$Q_{ss} = Q_n(1 + D + D') \tag{32}$$

where Q_{ss} is the steady-state blood flow to the brain, Q_n is the normal blood flow which was chosen to be 55 ml/min per 100 g of tissue, and D and D' express the oxygen and CO_2 dependence, respectively, as follows:

$$\begin{aligned} D &= 0, && P_a \geq 104 \text{ mm Hg}; \\ &= [2.785 - 0.1323P_a + (2.6032 \times 10^{-3})P_a^2 \\ &\quad - (2.324 \times 10^{-5})P_a^3 + (7.6559 \times 10^{-8})P_a^4]/0.75, && P_a < 104 \text{ mm Hg}; \end{aligned} \tag{33}$$

and

$$D' = [-15.58 + 0.7607P'_a - (1.2947 \times 10^{-2})P'^2_a + (9.3918 \times 10^{-5})P'^3_a - (2.1748 \times 10^{-7})P'^4_a]/0.75, \quad P'_a > 44 \text{ mm Hg};$$

$$= 0, \quad 38 \leq P'_a \leq 44 \text{ mm Hg};$$

$$= [(2.323 \times 10^{-2}) - (3.1073 \times 10^{-2})P'_a + (8.0163 \times 10^{-4})P'^2_a]/0.75, \quad P'_a < 38 \text{ mm Hg}. \tag{34}$$

Under dynamic conditions, the brain blood flow $Q(t)$ is assumed to be described by the first-order differential equation

$$dQ(t)/dt = (Q_{ss} - Q)/T, \tag{35}$$

where the time constant T was assumed to be 20 sec and Q_{ss} was given by equation (32). The blood flow to the remaining tissue group was then computed by first subtracting the brain blood flow from the cardiac output and then by assuming that muscle tissues receive 25%, and all other tissues 75%, of the remaining blood flow. The blood perfusion rates P_R for the three tissue groups were then obtained.

Experimentally obtained steady-state values of pH, oxygen and carbon dioxide tensions, concentrations of arterial blood, total body oxygen consumption, respira-

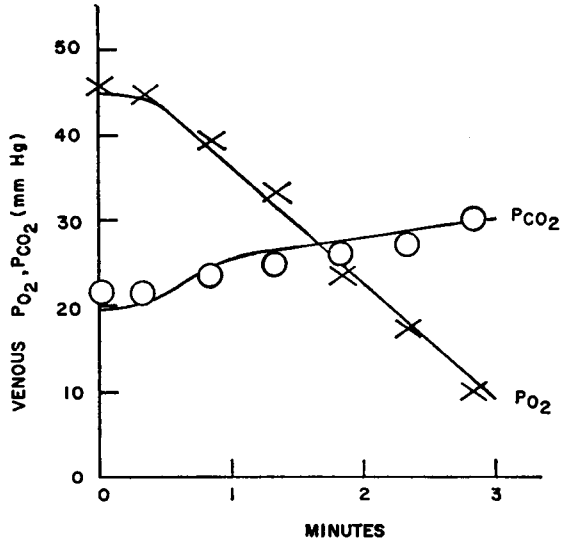

FIGURE 9 Comparison of computed (solid lines) and measured (×) mixed venous P_{O_2} and (○) P_{CO_2} during asphyxia in dog 4.

tory quotient, and body weight then were used to compute the "individual" parameters, i.e. the parameters which vary among animals, and the initial distribution in the three tissue compartments. Using the experimentally obtained arterial blood O_2 and CO_2 tensions and the experimental time-varying cardiac output as boundary conditions, the system equations 3–6 along with the dissociation equations were numerically integrated for each tissue group and O_2 and CO_2 tensions of the mixed venous blood were obtained from equations 7 and 8. Fig. 9 shows the mixed venous O_2 and CO_2 tensions as obtained in simulating the asphyxia experiment of dog 4. It is seen that there is good agreement between the analytical and experimental results.

The Complete System

The model of the complete system is obtained by combining all the equations describing each of the four subsystems. The first subsystem has been studied in detail in the last section and the values of its parameters have been discussed. With respect to the complete system, there are still four parameters to be evaluated, namely, the volume of blood in the pulmonary capillary bed V_B, the volume of the functional residual capacity of the lungs V_F of equations 20 and 21, the volume of arterial blood V_A in equation 23, and the volume of venous blood V_V in equation 24. Values for these parameters were obtained as follows. It is assumed that blood constitutes 8% of the body weight. The arterial blood is taken to be 20%, the venous blood 57%, and the pulmonary capillary blood 5% of the total blood (Gibson et al., 1946; Green, 1944; Kety, 1951; Yu, 1969). The remaining 18% is systemic capillary blood. The respective volumes are then obtained by assuming that the specific volume of blood is 1 ml/g. The value of V_F is chosen to be 40 ml for each kg of body weight (Cherniack et al., 1966, 1968).

It was also necessary to relate the cardiac output to the respiratory variables. In all of our experiments, the cardiac output during asphyxia increased at first to about 1.4 times its steady-state value and then either remained constant or, in some instances, decreased towards the end of the experiments. This change in cardiac output could be best approximated by relating the cardiac output Q_c to the arterial oxygen tension P_a as

$$Q_c(t) = Q_c(o), \qquad P_a(t) \geq 45 \text{ mm Hg};$$

$$Q_c(t) = Q_c(o)\{1 + 0.02[45 - P_a(t)]\}, \qquad P_a(t) < 45 \text{ mm Hg},$$

with the limiting constraint that $Q_c(t) \leq 1.4\ Q_c(o)$ where $Q_c(o)$ is the steady-state cardiac output at the beginning of the experiment.

The rate of ventilation $\dot{V}(t)$, also needed for the mathematical simulation, is zero during the asphyxia experiments. In order to simulate specific experiments, the weight of the animal, total steady-state O_2 consumption, over-all steady-state respiratory quotient, steady-state cardiac output, steady-state arterial blood pH and

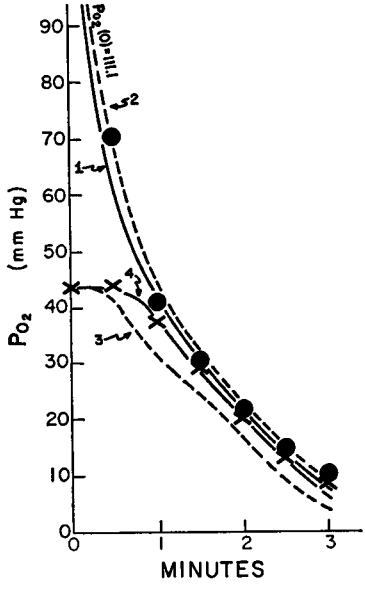

FIGURE 10 *a*

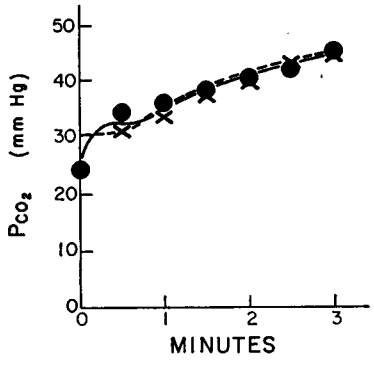

FIGURE 10 *b*

FIGURE 10 Comparison of experimental and computed results during asphyxia in dog 5. (*a*) The four curves in Fig. 10 *a* show the computed time courses of blood P_{O_2} during asphyxia at four different locations in the body, namely (1) blood exiting the lungs, (2) blood entering tissue, (3) end capillary mixed venous blood, and (4) venous blood entering the lungs. Curve 2 lags curve 1 by a time-varying arterial transport delay and curve 4 lags curve 3 by a time-varying venous transport delay. Experimental arterial P_{O_2} (●) lies between curves 1 and 2 and experimental venous P_{O_2} (×) between curves 3 and 4. (*b*) Fig. 10 *b* shows the corresponding experimental and computed blood P_{CO_2}. Because of the small CO_2 tension gradient in arterial and venous blood, only one arterial and one venous P_{CO_2} curve are shown. ●'s indicate measured arterial P_{CO_2} and ×'s, measured venous P_{CO_2}.

O_2 and CO_2 tensions and concentrations, and the barometric pressure, which were measured experimentally, were used as inputs. Some results of simulating asphyxia experiments are shown in Figs. 10 *a* and *b* for dog 5. Additional results are given in Trueb (1970). Figs. 10 *a* and *b* show the computed arterial and venous O_2 and CO_2 tensions at different sites in the circulatory system. It can be seen that the complete model reproduces both arterial and mixed venous gas tensions during asphyxia based on the initial steady-state values.

DISCUSSION

The level of ventilation can be considered to be a function of the O_2 and CO_2 tensions existing at the site of the respiratory chemoreceptors. The level of these gas tensions depends, in turn, on the response of the controlled plant, i.e. the amount and distribution of O_2 and CO_2 in the blood and tissues, to a disturbance such as O_2 or CO_2 addition to or removal from the body. The properties of the controlled plant are a major factor in determining the rate at which ventilation changes when

different gas mixtures are inspired since the transmission of nerve impulses from the chemoreceptors to the respiratory center and then to the respiratory muscles is extremely rapid requiring only a few milliseconds. Therefore, accurate modeling of the controlled plant is needed in models of the respiratory control system.

In the present study a mathematical model of the controlled plant is developed which describes gas exchange across the tissue–systemic capillary interfaces, across the alveolar air-pulmonary capillary junction, and the transportation of CO_2 and O_2 between these two sites of gas transfer. Particular emphasis is placed in this model on gas exchange across systemic capillaries since this process appears to play a major role in determining the dynamic behavior of the controlled plant. Since the body tissues vary with respect to many of the parameters involved in gas exchange (e.g. metabolism, capillary density), the body tissues are subdivided into three parts corresponding to the brain, muscles, and the remainder of the body tissues. Because O_2 and CO_2 do not diffuse instantaneously either between or within blood and tissues the model takes into account the variations in gas tensions which occur after a change in ventilation, both with respect to time and location along the vascular bed. The accuracy of this portion of the model dealing with gas exchange across systemic capillaries was verified separately. Arterial inflow gas tensions and concentrations during arrested ventilation were used to predict both muscle venous and mixed venous gas tensions. When satisfactory simulation of experimental results by this segment of the mathematical model was achieved, the model of the controlled plant was completed. Starting from initial steady-state conditions, the completed model of the controlled plant was able to reproduce with reasonable accuracy both the arterial and venous O_2 and CO_2 tensions measured experimentally during asphyxia.

Uncertainty about the actual value of some of the parameters used in this model was the major difficulty encountered. The most uncertain of these parameters are the blood-to-tissue volume ratio, V_R, which is related to the density of open capillaries in the tissue, and the parameters k and k', which determine the resistance to O_2 and CO_2 transfer in vivo. This difficulty was partially circumvented since parameter variations in the model showed that the product of V_R and k or k', rather than the exact value of each, is the principal determinant. Experimental data obtained from measurements in muscle tissue in several dogs during asphyxia and apneic oxygenation could be accurately simulated if the values of V_R, k, and k' were chosen so that the resulting tension differences in the steady state between blood and tissue were about 20 mm Hg for O_2 and 3.5 mm Hg for CO_2. These conditions are satisfied if the parameter V_R increased in proportion to the metabolic rate, a phenomenon which has substantial experimental support (Krogh, 1919; Otis, 1963; Stainsby and Otis, 1964). The assumption of a steady-state gradient of 20 mm Hg for O_2 between capillary blood and tissues agrees with the estimate of the O_2 tension gradient made by Stainsby and Otis (1964) from experiments in which they measured muscle O_2 consumption in dogs rebreathing oxygen. This estimate of the O_2 gradient is also compatible with measurements of tissue O_2 tension made by Cater et al. (1961) and by Jamieson and von den Brenk (1965) using electrodes, although measurements

made by other investigators also using tissue electrodes suggest a somewhat greater gradient (Whalen and Nair, 1967).

A CO_2 tension gradient in the steady state of 3.5 mm Hg between the blood and tissues successfully reproduced experimentally measured muscle venous CO_2 tensions in this model when the muscle was assigned a buffering capacity for CO_2 comparable to that of water. Steady-state measurements in muscle indicate that muscle buffering capacity is probably considerably greater than the value assigned (Clancy and Brown, 1966). If this greater buffering capacity had been used in making computations, experimental results could be duplicated by the model only by increasing the resistance to CO_2 diffusion between capillary blood and muscle. Although only a few measurements of CO_2 diffusivity in tissues have been made either in vivo or in vitro, these results indicate that a steady-state gradient between capillaries and tissues greater than 3.5 mm Hg is improbable. Taken together, these findings seem to indicate that muscle is unable to exert its full buffering capacity for CO_2 for reasons other than restricted diffusion. They also increase the likelihood, as suggested previously, that slow chemical reactions such as those involved in CO_2 buffering in muscle may prevent muscular tissue from exerting its full buffering potential (Cherniack et al., 1966, 1968).

The mathematical model presented is more complex than many previous models, but it is less complex than the actual controlled plant. Of necessity, simplifying assumptions were made. Although these assumptions were based either on experimental evidence or mathematical reasoning, and therefore seem justified, their exact effects on computed results are difficult to evaluate precisely. Despite these assumptions, the proposed model seems to accurately reproduce the dynamic behavior of the controlled plant; deviations between measured and theoretical values lie well within the range of experimental accuracy. Also, the introduction of the distributed parameter approach seems to contribute to the flexibility of the model of the controlled plant in predicting gas tensions both in specific tissues as well as in the body as a whole.

The ability of the model presented to predict gas tensions in muscle may make it particularly useful as a component of a model of respiratory control during exercise where changes in muscle gas tensions may contribute to ventilatory drive (Dejours, 1967). The distributed parameter approach used in the present study also allows gas tensions to be predicted along the length of the vascular system. Therefore, the model presented may also be of special value in describing distributions of blood flow to organs and the microcirculation under the influence of local gas tensions.

This paper is based, in part, on a thesis submitted by T. J. Trueb, in partial fullfillment of requirements for the degree of Doctor of Philosophy in Mechanical and Aerospace Engineering, Illinois Institute of Technology, October, 1969.

Dr. N. S. Cherniack is a Career Development Awardee of the National Heart and Lung Institute (HE-17792).

This study was supported by grants from the National Heart and Lung Institute, HE-10979, HE12962, and HE08805, and by U. S. Public Health Service grant HE-12962-01.

Received for publication 6 November 1970.

REFERENCES

BAILEY, H. R. 1967. *In* Physical Bases of Circulatory Transport: Regulation and Exchange. E. B. Reeve and A. C. Guyton. editors. W. B. Saunders Company, Philadelphia. 353.

BARCROFT, J., and T. KATO. 1919. *Phil. Trans. Roy. Soc. London Ser. B. Biol. Sci.* **207**:149.

CATER, P. B., S. GORATTINI, F. MORENA, and I. A. SILVER. 1961. *Proc. Roy. Soc. Ser. B. Biol. Sci.* **155**:136.

CHERNIACK, N. S., G. S. LONGOBARDO, F. P. PALERMO, and M. HEYMAN. 1968. *J. Appl. Physiol.* **24**:809.

CHERNIACK, N. S., G. S. LONGOBARDO, I. STAW, and M. HEYMAN. 1966. *J. Appl. Physiol.* **21**:785.

CLANCY, R. L., and E. BROWN, JR. 1966. *Amer. J. Physiol.* **211**:1309.

COBURN, R. F., and L. MAYERS. 1968. *J. Clin. Invest.* **47**:21a.

DEFARES, J. G., H. DERKSEN, and J. W. DUYFF. 1960. *Acta Physiol. Pharmacol. Neer.* **9**:327.

DEJOURS, P. 1967. *Circ. Res.* **20**(Suppl. 1):146.

DRABKIN, D. L. 1951. *Physiol. Rev.* **31**:345.

FARHI, L. E., and H. RAHN. 1960. *Anesthesiology.* **21**:604.

FLUMERFELT, R. W., and E. D. CRANDALL. 1968. *Math. Biosci.* **3**:205.

FOWLE, A. S. E., and E. J. M. CAMPBELL. 1964. *Clin. Sci. (London).* **27**:41.

GIBSON, J. C., A. M. SELIGMAN, W. C. PEACOCK, J. C. OUT, J. FINE, and R. D. EVANS. 1946. *J. Clin. Invest.* **25**:848.

GOMEZ, D. M. 1960. *Amer. J. Physiol.* **200**:135.

GREEN, H. D. 1944. *In* Medical Physics. D. Glasser, editor. Year Book Medical Publishers, Inc., Chicago. **2**:228.

GRODINS, F. S., J. BUELL, and A. J. BART. 1967. *J. Appl. Physiol.* **22**:260.

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

HAMILTON, W. F., R. L. RILEY, A. M. ATTYAH, A. COURNAND, D. M. FOWELL, A. HIMMELSTEIN, R. P. NOBLE, J. W. REMINGTON, D. W. RICHARDS, N. C. WHEELER, and A. C. WITHAM. 1948. *Amer. J. Physiol.* **153**:309.

HORGAN, J. D., and R. L. LANGE. 1965. *Biophys. J.* **5**:935.

JAMIESON, D., and H. S. VON DEN BRENK. 1965. *J. Appl. Physiol.* **20**:514.

KETY, S. S. 1951. *Pharmacol. Rev.* **3**:41.

KROGH, A. 1919. *J. Physiol. (London).* **52**:409.

LONGOBARDO, G. S., N. S. CHERNIACK, and A. P. FISHMAN. 1966. *J. Appl. Physiol.* **21**:1839.

LONGOBARDO, G. S., N. S. CHERNIACK, and I. STAW. 1967. *I.E.E.E. (Inst. Elec. Electron. Eng.) Trans. Bio-Med. Eng.* BME **14**:182.

MAREN, T. H. 1967. *Physiol. Rev.* **47**:595.

MATTHEWS, C. M. E., G. LASZLO, E. J. M. CAMPBELL, and D. J. C. READ. 1968/1969. *Resp. Physiol.* **6**:45.

MILHORN, H. T., JR., R. BENTON, R. ROSS, and A. D. GEUYTON. 1965. *Biophys. J.* **5**:27.

OTIS, A. B. 1963. *In* The Regulation in Human Respiration. D. J. C. Cunningham and B. B. Lloyd, editors. Blackwell Scientific Publications Ltd., Oxford. 111.

PAPPENHEIMER, J. R. 1953. *Physiol. Rev.* **33**:387.

RENKIN, E. M., O. HUDLICKA, and R. M. SHEEHAN. 1966. *Amer. J. Physiol.* **211**:87.

ROUGHTON, F. J. 1964. *In* Handbook of Physiology. Sec. 3: Respiration. American Physiological Society, Washington D.C. **1**:790.

SPECTOR, W. S., editor. 1956. Handbook of Biological Data. W. B. Saunders Company, Philadelphia.

STAINSBY, W. N., and A. B. OTIS. 1964. *Amer. J. Physiol.* **206**:858.

STAW, I. 1968. Dynamics of mammalian carbon dioxide stores. Ph.D. Thesis. Columbia University, New York.

TENNEY, S. M., and T. W. LAMB. 1964. *In* Handbook of Physiology. Sec. 3: Respiration. American Physiological Society, Washington, D.C. **2**:979.

TRUEB, T. J. 1970. A distributed parameter model of the respiratory control system. Ph.D. Thesis. Illinois Institute of Technology, Chicago.

WHALEN, W. J., and P. NAIR. 1967. *Circ. Res.* **21**:251.

YU, P. N. 1969. Pulmonary Blood Volume in Health and Disease. Lea & Febiger, Philadelphia.