PROGRESS REPORT
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CONCEPTUAL IDEA OF DIGITAL COMPUTER MODEL OF HUMAN RESPIRATORY SYSTEM

-By-

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CONTENTS

PROGRESS REPORT

I. INTRODUCTION. In the development of a digital computer model of the human respiratory system two types of research are presently being pursued. These are (1) simulation and (2) experimental. The simulation work is primarily to extend and improve the controlled system, specifically the pulmonary system. The experimental work concerns the controller equations for ventilation and cardiac output. A detailed discussion of both of these (simulation and experimental) is impractical. Some of the more important aspects, however, are discussed in the material which follows:

II. SIMULATION

A. Static Respiratory System Model: In order to become more familiar with existing respiratory controller equations, a study of the steady-state respiratory system is being carried on. Two controller equations are being investigated. The first is the classical equation of Gray (1950)

$$\dot{V}_A = a P_{A_{CO_2}} - b + c(d - P_{A_{O_2}})^n \geq 0 \qquad (1)$$

in which $\dot{V}_A$ is alveolar ventilation, $P_{A_{CO_2}}$ is alveolar CO_2 partial pressure, $P_{A_{O_2}}$ is alveolar O_2 partial pressure, and a, b, c, d, and n are empirical constants. Equation (1) is being compared to the more recent equation of Lloyd and Cunningham (1963)

$$\dot{V} = D(P_{A_{CO_2}} - B)\{1 + A/(P_{A_{O_2}} - C)\}^3 ; P_{A_{CO_2}} \geq 40 \qquad (2)$$

in which $\dot{V}$ is minute pulmonary ventilation and A, B, C, and D are empirical constants. Minute deadspace fV_D must be subtracted form $\dot{V}$ to give $\dot{V}_A$ for equation (2). This equation, it should be noted, is good only for $P_{A_{CO_2}} \geq 40$ mm Hg. Experimental work to determine the portion of the controller equation in the range $P_{A_{CO_2}} < 40$ mm Hg is presently being carried on and will be discussed later.

The controlled system equations used are theoretical and have been derived by several persons (Otis 1964).

$$P_{A_{CO_2}} = P_{I_{CO_2}} + \frac{\dot{V}_{CO_2}}{\dot{V}_A}(P_B - P_{H_2O}) + P_{I_{CO_2}}\left(\frac{1}{R} - 1\right)\frac{\dot{V}_{CO_2}}{\dot{V}_A} \qquad (3)$$

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{\dot{V}_{O_2}}{\dot{V}_A}(P_B - P_{H_2O}) + P_{I_{O_2}}(1 - R)\frac{\dot{V}_{O_2}}{\dot{V}_A} \qquad (4)$$

$P_{I_{CO_2}}$ and $P_{I_{O_2}}$ are the inspired CO_2 and O_2 partial pressures, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ are the CO_2 production and O_2 consumption rates, P_B is barometic pressure, P_{H_2O} is water vapor pressure, and R is the respiratory quotient.

A block diagram of the steady-state respiratory control system is shown in figure 1.

This analysis will yield results for a variation of the following parameters: $P_{I_{O_2}}$, $P_{I_{CO_2}}$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, P_B, and R. In addition, shifts in the parameter values of the controller equations are being studied as relating to specific conditions. B, for instance, reflects a shift in the acid-base status of the individual.

Parameter variation in this model, using a digital computer, is presently being carried on.

B. Dynamic Respiratory System Model. In a previous study (Milhorn et al., 1965) the chemical control of respiration was simulated using a digital computer. The

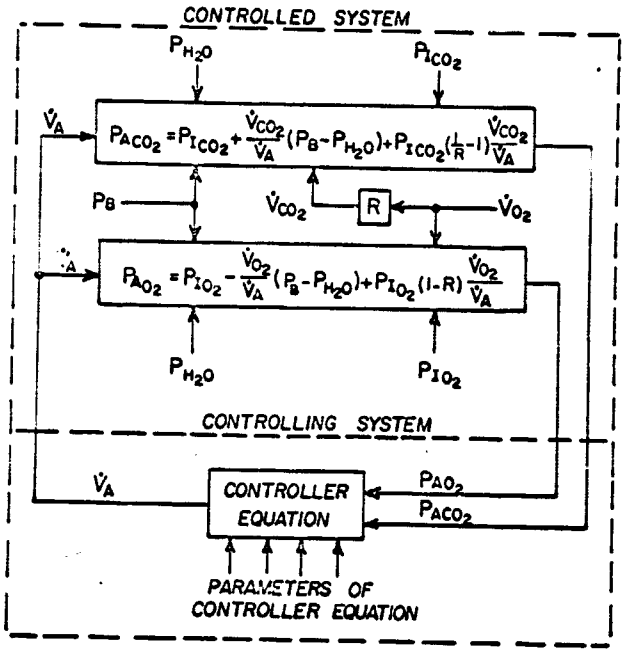

CONTROLLED SYSTEM
P_{H_2O}
P_{ICO_2}
$\dot{V}_A$
$P_{ACO_2} = P_{ICO_2} + \frac{\dot{V}_{CO_2}}{\dot{V}_A}(P_B - P_{H_2O}) + P_{ICO_2}(\frac{1}{R} - 1)\frac{\dot{V}_{CO_2}}{\dot{V}_A}$
P_B
$\dot{V}_{CO_2}$
R
$\dot{V}_{O_2}$
$\dot{V}_A$
$P_{AO_2} = P_{IO_2} - \frac{\dot{V}_{O_2}}{\dot{V}_A}(P_B - P_{H_2O}) + P_{IO_2}(1-R)\frac{\dot{V}_{O_2}}{\dot{V}_A}$
P_{H_2O}
P_{IO_2}
CONTROLLING SYSTEM
$\dot{V}_A$
CONTROLLER EQUATION
P_{AO_2}
P_{ACO_2}
PARAMETERS OF CONTROLLER EQUATION

FIGURE 1

major aspects of this model are described in the following: The model consisted of three compartments (brain, lungs, and lumped tissue). Ventilation was considered to be a continuous perfusion rather than breath-by-breath, H^+ was considered to be function of P_{co_2}, cardiac output was considered to remain constant, cerebral blood flow was assumed to be the sum of a CO_2 effect and an assumed O_2 effect, circulation times were considered to be constant, ventilation was assumed to be the sum of an arterial blood O_2 effect and a brain tissue CO_2 effect, CO_2 dissociation curves of blood and tissue were assumed to be the same, alveolar P_{co_2} was assumed to be in equilibrium with end-alveolar capillary P_{co_2}, alveolar P_{o_2} was assumed to differ from end-alveolar capillary P_{o_2} by an empirical amount ($Pao_2 = K\ P_{Ao_2}$), and cerebrospinal fluid effects were not considered. An extension of this model is presently in progress which alters many of the major assumptions of the model to make it more realistic. One of the major problems in all respiratory simulation studies has been the correct form of the ventilatory controller equation. In the new model, this is handled as follows:

When a subject is allowed to breath a mixture high in CO_2, the arterial H^+ rises as does ventilation. On the other hand, when a subject is infused with a fixed acid such as HCl, the H^+ rises as does ventilation, but CO_2 decreases. If the H^+ is raised to the level it attained in the CO_2 breathing experiment and the arterial CO_2 is held constant by increasing the inspired CO_2 to the correct concentration, ventilation increases about 55 per cent of the CO_2 inhalation value (Comroe, 1964). This has been interpreted as meaning that 55 per cent of the ventilatory drive is due to H^+ and 45 per cent to CO_2. Thus both are indicated as direct respiratory

stimuli. Recent experiments by Lambertsen (1966) have given this another interpretation. By analyzing the "off" transient to a step of CO_2 in inspired air he found that the ventilatory response could be broken down into three components as follows:

	Dead Time	Half-time	Percent of Response
(1)	4 sec	short	12
(2)	16 sec	medium	44
(3)	16 sec	long	44

TABLE I

The first component can be considered to be the CO_2 response of the peripheral chemoreceptors, since it has a 4 second dead time and a rapid response. The second and third can be considered to be intracranial receptors, since the dead time is 16 seconds. The medium response receptor can be considered to be a receptor on the blood side of the blood-brain barrier, and the slow response can be considered to be a receptor on the cerebrospinal fluid side of the blood-brain barrier. From the viewpoint of modeling, this last interpretation is the most appealing. Using Winterstein's reaction theory (1956) and the assumption that the H^+ components are additive, the H^+ portion of the controller equation can be written

$$\dot{V} = 0.12\dot{V}(C_{ps_{H^+}}) + 0.44\dot{V}(C_{B_{H^+}}) + 0.44\dot{V}(C_{csf_{H^+}}) \quad (5)$$

in which $0.12\dot{V}(Cp_{s_{H^+}})$ is the ventilatory contribution from the peripheral sensors, $0.44\dot{V}(C_{B_{H^+}})$ is the ventilatory contribution from the central receptor on the blood side of the blood-brain barrier, and $0.44\dot{V}(Ccsf_{H^+})$ is the ventilatory contribution from the central receptor on the cerebrospinal fluid side of the blood-brain barrier.

These functions, as well as the peripheral O_2 sensor function, are obtained as follows: The model is developed completely, with the exception of the controller equation. The steady-state equations are then rearranged so that the inputs are $\dot{V}$, $P_{A_{CO_2}}$, and $P_{A_{O_2}}$ and the outputs are $C_{ps_{O_2}}$, $C_{ps_{H^+}}$, $C_{B_{H^+}}$, and $C_{csf_{H^+}}$ as shown in figure 2. Experimental sets of inputs are then put into the model and the corresponding sets of outputs are obtained. For the H^+ portion, the H^+ concentration of each sensor is plotted against $\dot{V}$. These functions are then multiplied by their fractional contribution to give $\dot{V}$ as shown by equation (5). It is expected that the O_2 portion will be similar in form to the Lloyd and Cunningham equation previously discussed.

An extensive review of the literature for data useful in extending the present model, as well as testing it, is presently being carried on.

C. Concentration Gradients Along Pulmonary Capillaries. In a previous study (Milhorn and Pulley, 1968) a theoretical study of pulmonary capillary gas exchange was developed and the normal state and the state of low O_2 inhalation were simulated. This model is presently being extended as follows: The previous model was restricted essentially to $P_{I_{O_2}}$ normal because of the form of the O_2 dissociation curve used. Both the O_2 and CO_2 dissociation curves were fitted with empirical equations which required tabulated parameter values. In the extended version of the model, the dissociation curves have been fitted with easier to work with formulas. In addition, pH has been included in the new version. The new dissociation curves are as follows:

$$C_{CO_2} = f_1(P_{O_2})(P_{CO_2})^{k_2} \tag{6}$$

$$C_{O_2} = 0.2\left(1 - EXP(-f_2(pH)P_{O_2})\right)^2 + \alpha_{O_2}/P_B \tag{7}$$

$$pH = pK + LOG\left[1.17C_{CO_2} - (\alpha_{CO_2}/P_B)P_{CO_2}\right]/(\alpha_{CO_2}/P_B)P_{CO_2} \tag{8}$$

The functions $f_1(P_{O_2})$ and $f_2(pH)$ are calculated curves which are fitted with straight line segements for the computations. k_1 and k_2 are empirical constants, (α_{O_2}/P_B) and

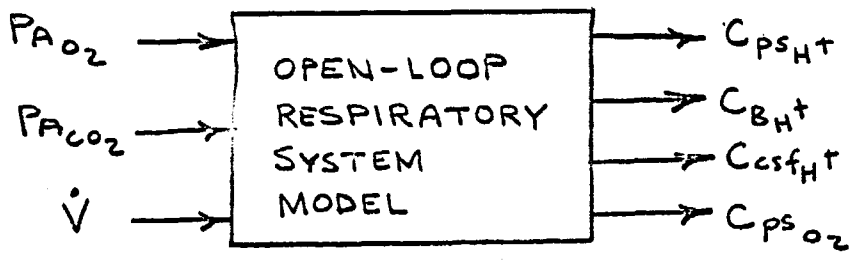

$P_{A_{O_2}}$
$P_{A_{CO_2}}$
$\dot{V}$
OPEN-LOOP
RESPIRATORY
SYSTEM
MODEL
$C_{ps_{H^+}}$
$C_{B_{H^+}}$
$C_{csf_{H^+}}$
$C_{ps_{O_2}}$

FIGURE 2

(α_{CO_2}/P_B) are solubility coefficients expressed per mm Hg. $P_{A_{O_2}}$ and $P_{A_{CO_2}}$, which were treated as constants in the previous study, are allowed to fluctuate now according to data from the literature.

The diffusing capacity of the pulmonary membrane is altered in several situations, including CO_2 inhalation and exercise. This is caused by a change in effective diffusing area of the pulmonary membrane and can be caused by either new capillaries opening up due to increased blood flow or new alveoli opening up due to increased lung volume. It is tentatively planned to simulate this condition as follows:

$$A = A_o + \frac{1}{k_1 + k_2}\left(k_1 \frac{V_L}{V_{L_o}} + k_2 \frac{\dot{Q}_c}{\dot{Q}_{c_o}}\right) \qquad (9)$$

in which A_o is the normal effective area, V_L is lung volume, $\dot{Q}_c$ is total blood flow through the pulmonary capillaries, and k_1 and k_2, are constants which are to be determined from experimental data.

Normal gradients along the capillary are computed for various positions during the normal breathing cycle. The gradients are studied for a variation of parameters in the model. These parameters consist of cardiac output, shunt flow, pulmonary capillary surface area, and pulmonary membrane thickness.

A computer program for this extended model is presently being written.

D. Mechanical Dynamics Model. In 1966, Jodat et al. published a linear model of the mechanical dynamics of respiration. This model was limited to normal breathing only. An extension of this model is presently in progress to allow it to hold for the general case, rather than for just normal breathing. To do this, function curves of the compliances of the lungs and thorax are being used in place of the original constants. This means that the compliances are now a function of the respective volumes. Resistance of the respiratory airways are included. Resistance automatically increases and decreases with expiration and inspiration as pleural pressure changes.

The nonlinear flow pattern

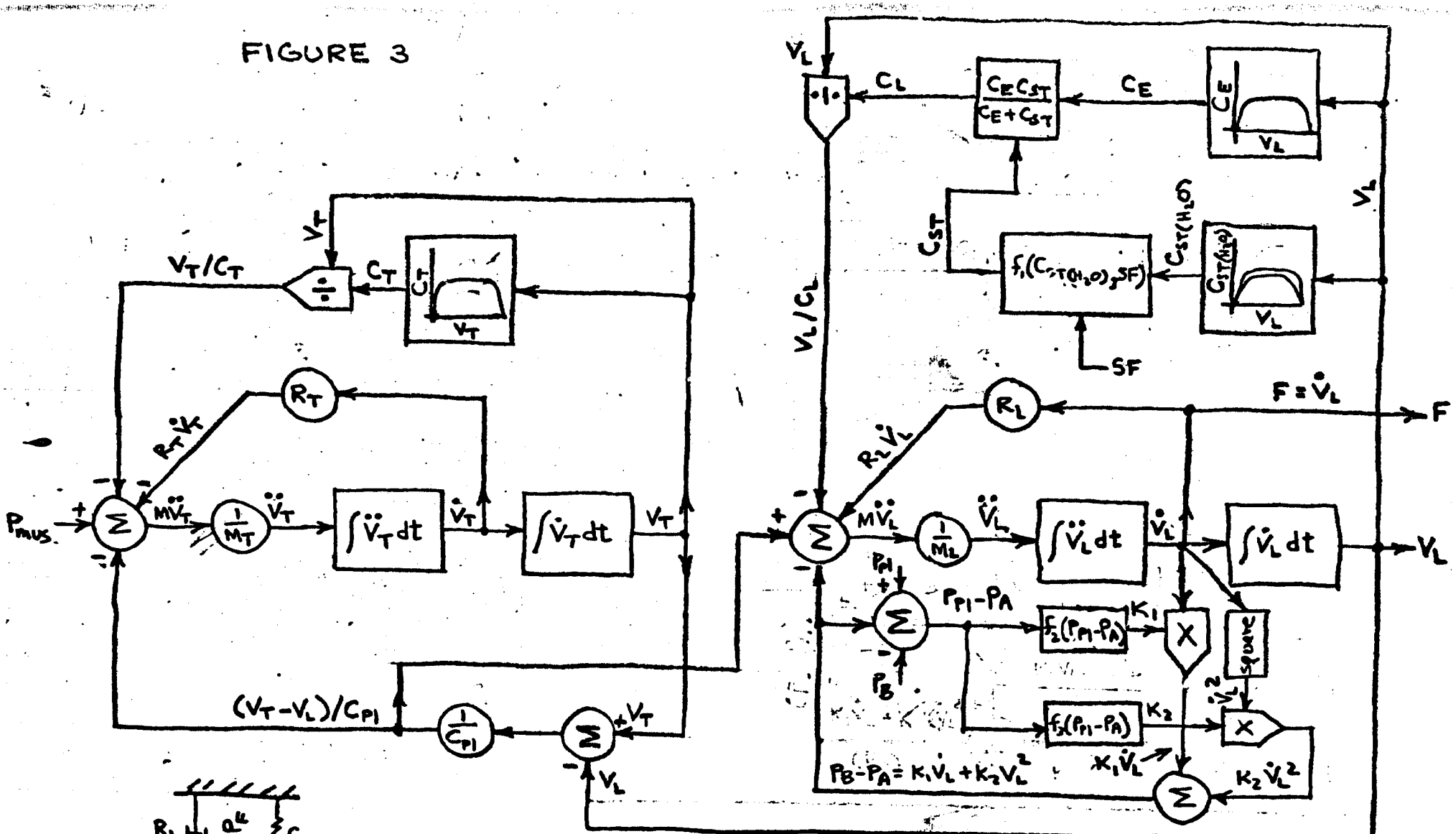
$$P_B - P_A = K_1 F + K_2 F^2 \qquad (10)$$

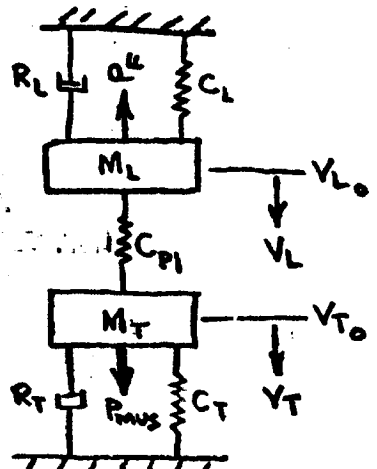
is also included. K_1 and K_2 are functions of resistance and F is airflow. The first term is for laminar flow and the second is for turbulent flow. In addition, lung compliance is broken down into its elastic and surface tension components. The effects of alteration of the surfactant concentration on mechanical dynamics is studied. The extension of the model also allows study of the effects of a sudden pneumothorax on mechanical dynamics. A block diagram of the mechanical system is shown in figure 3. The diagram in the lower left hand portion is a linear representation of the system. Although a linear representation of a system such as this is a good qualitative aid in thinking about the system, it hides many nonlinear aspects as shown by the block diagram.

A literature survey for data which might be useful in developing and testing this model is presently being carried on.

E. Breath-by-breath pulmonary system model. Recent experiments (Dutton, et al) have indicated the possibility of unidirectional rate sensitivity existing in the peripheral chemoreceptors. Although the importance of this in normal breathing is in doubt, it appears that it could possibly be of importance during exercise when the arterial blood $C_{a_{H^+}}$, $C_{a_{CO_2}}$, and $C_{a_{O_2}}$ are fluctuating rapidly. For this reason, a breath-by-breath pulmonary system model is being developed to accurately simulate these fluctuations. This system is shown diagramatically in figure 4. The muscle generated pressure (Pmus) acts on the thorax to expand and relax it during the breathing cycle. This alters the pleural pressure P_{p_1} which causes the lungs to expand and relax, which alters the alveolar pressure. Atmospheric pressure minus alveolar

FIGURE 3





P_{mus} = muscle generated pressure
R = resistance
C = compliance
M = mass
V = volume
SF = surfactant concentration

T = thorax
pl = pleural
L = lung
E = elastic
ST = surface tension of alveoli
ST(H_2O) = bubble surface tension of H_2O

K_1 & K_2 = parameters which are functions of Newtonian & turbulent flow

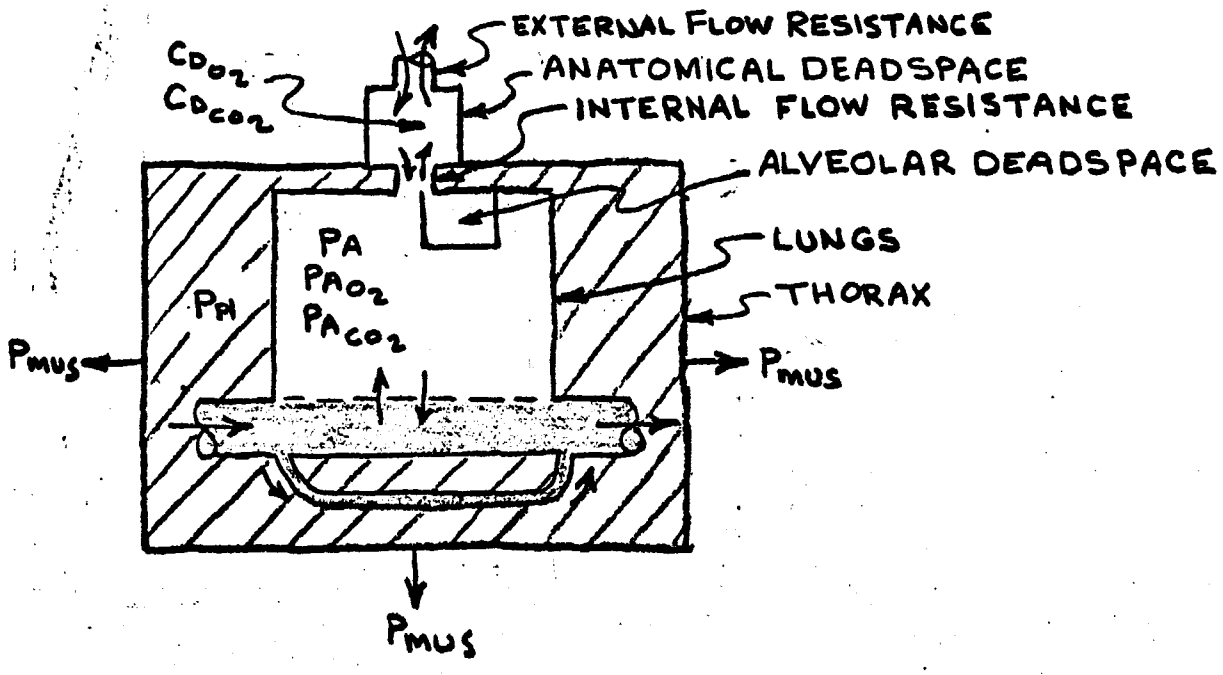

EXTERNAL FLOW RESISTANCE
ANATOMICAL DEADSPACE
INTERNAL FLOW RESISTANCE
ALVEOLAR DEADSPACE
LUNGS
THORAX
$C_{D_{O_2}}$
$C_{D_{CO_2}}$
P_A
$P_{A_{O_2}}$
$P_{A_{CO_2}}$
P_H
P_{MUS}
P_{MUS}
P_{MUS}

FIGURE 4

pressure causes air to flow into and out of the lungs at a rate dependent upon the resistance to air flow. The resistance is composed of two parts. The first is an external resistance (upper airway) which is fixed and an internal resistance (small bronchioles) which varies during the breathing cycle with $P_{p_1} - P_A$. The anatomical deadspace is the portion of the total deadspace made up of air passageways. The alveolar deadspace is the portion of the total deadspace made up of alveoli which are ventilated but not perfused by blood. Blood entering the lungs divides into two portions as shown. The major portion passes through the alveolar capillaries and exchanges gases with the alveoli. A smaller portion bypasses the alveoli to cause the venous-admixture effect. This portion is composed of several components, including direct a-v shunts and capillaries which perfuse unventilated alveoli.

The relationship between different parts of the pulmonary system are shown in figure 5. Two parts, the mechanical dynamics model and the capillary gas exchange model, have already been discussed. These interact with the alveoli and deadspace part and the venous admixture part as shown. This model is in the development stage.

III. EXPERIMENTAL

A. Cardiovascular. One of the major unknowns in respiratory system simulation concerns circulatory dynamics. The experiment discussed here is designed to study the dynamics of cardiac output in response to steps of low oxygen in inspired air. Cardiac output (aortic flow) is continously monitored by a cronically implanted electromagnetic flow probe and arterial and mixed venous blood samples are taken at fixed intervals from cronically implanted catheters. A pilot study in one dog is shown in figure 6. From data such as these it is hoped to determine a cardiac output controller equation.

Experiments in this study are in progress.

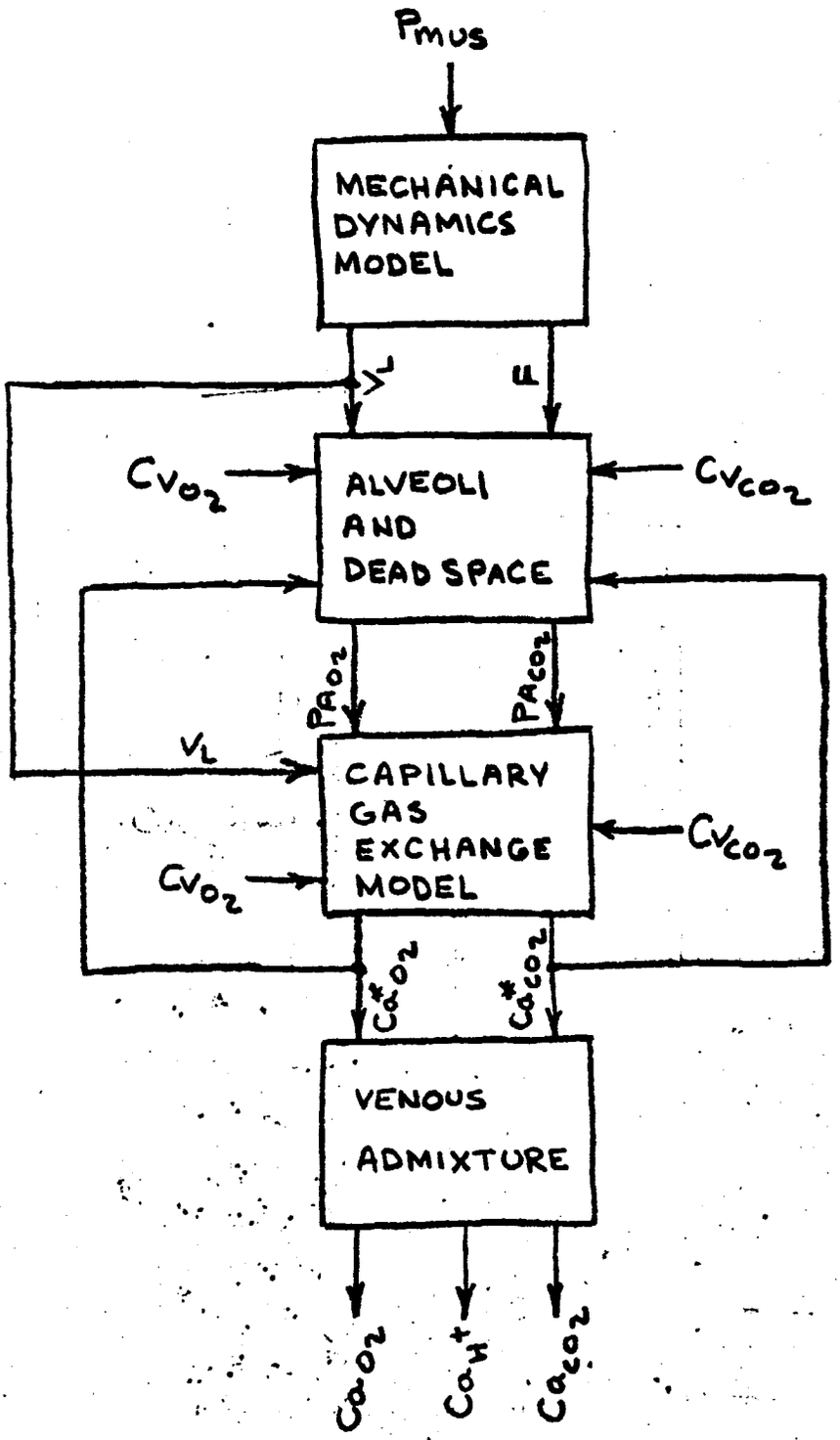

Pmus
MECHANICAL DYNAMICS MODEL
V
u
CvO2
ALVEOLI AND DEAD SPACE
CvCO2
PAO2
PACO2
VL
CAPILLARY GAS EXCHANGE MODEL
CvCO2
CvO2
C*aO2
C*aCO2
VENOUS ADMIXTURE
CaO2
CaH+
CaCO2

FIGURE 5

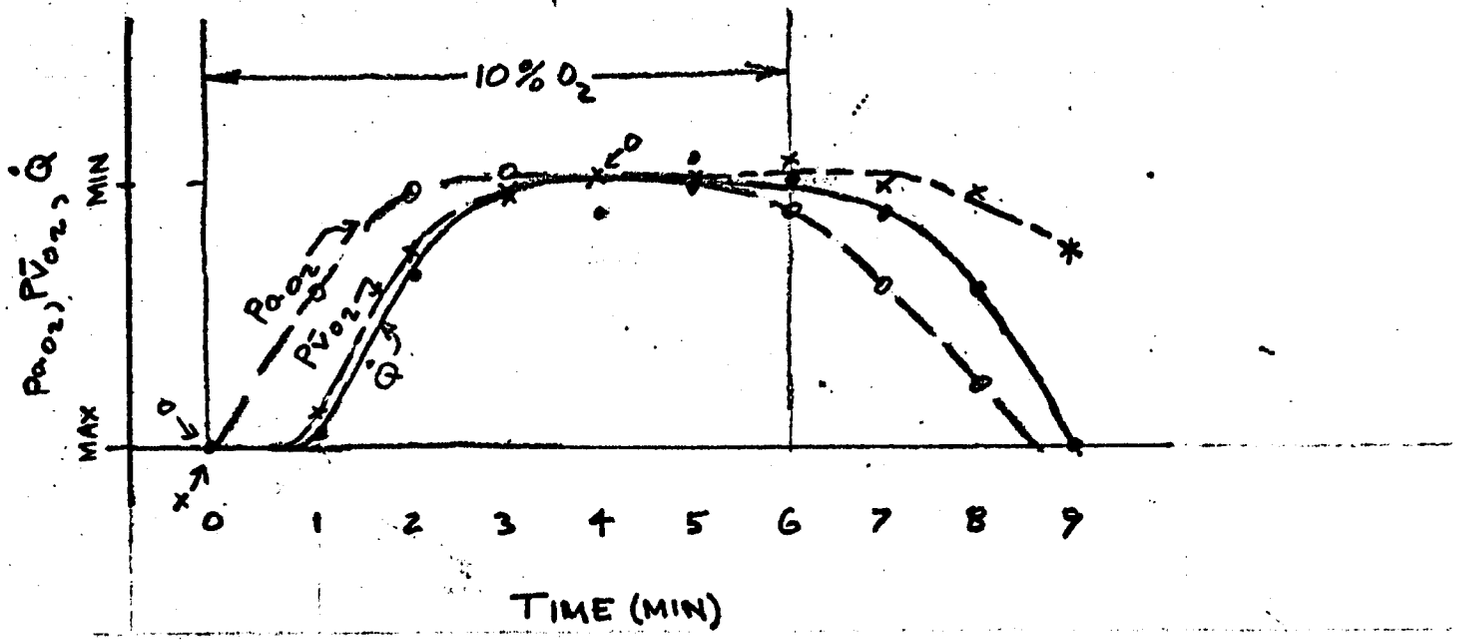
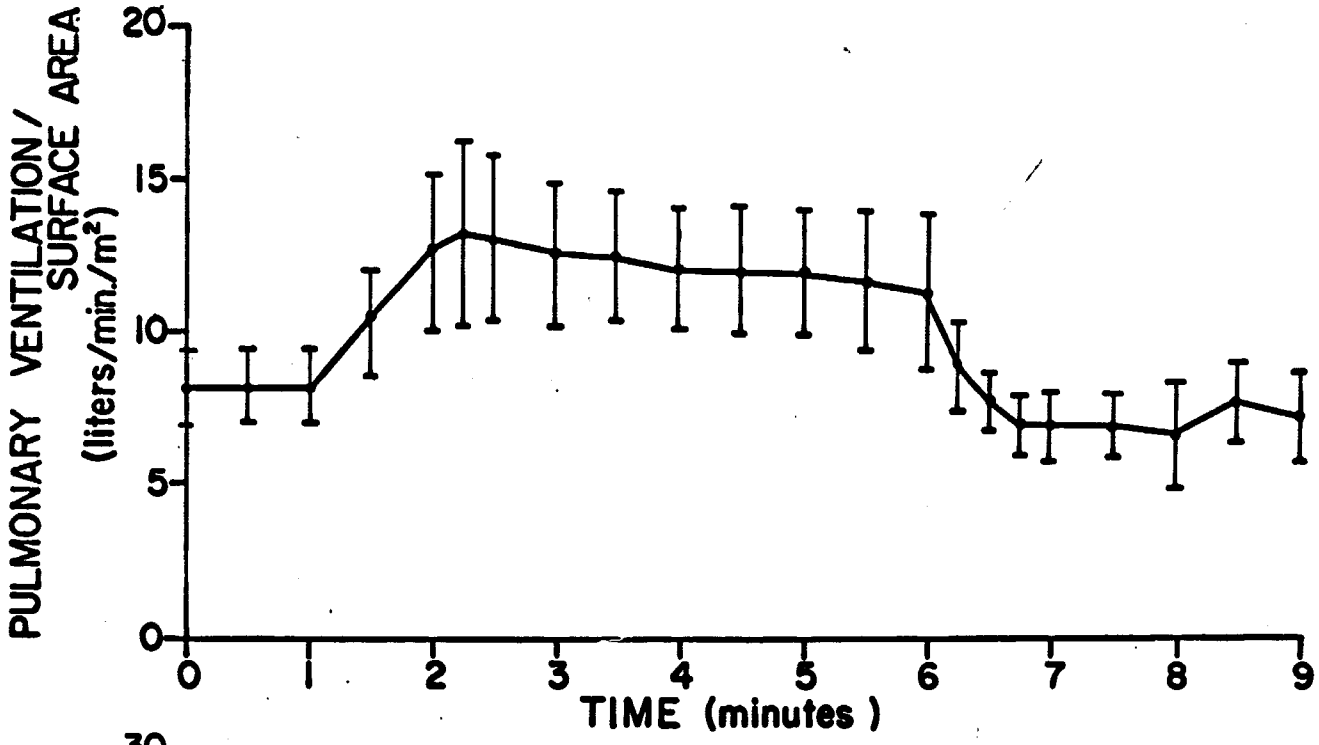

10% O_2
P_{aO_2}, $P\bar{v}_{O_2}$, $\dot{Q}$
MIN
MAX
P_{aO_2}
$P\bar{v}_{O_2}$
$\dot{Q}$
0
1
2
3
4
5
6
7
8
9
TIME (MIN)

FIGURE 6

B. Respiratory. As mentioned previously, the controller equation of Lloyd and Cunningham is limited to the $P_{A_{co_2}} \geq 40$ mm Hg range, although it holds for all values of $P_{A_{o_2}}$. An experiment is presently being carried on which has as its intent the development of an empirical model of the range $P_{A_{co2}} < 40$ mm Hg. The basic component of this experiment is a servo-system which is described in the attached reprint (Holloman, Milhorn, and Coleman, 1968).

The results of a step in room air to 9 per cent oxygen and back again are shown in figure 7 of this progress report. The upper trace is the average of five human subjects when alveolar CO_2 is not controlled. The lower trace is the average of the same five subjects when their alveolar CO_2 is controlled at their normal value. Figures 8, 9, and 10 show the responses of alveolar CO_2, tidal volume, and frequency in the same individuals. It can be seen from these two traces that the influence of P_{Aco_2} 40 mm Hg is of considerable importance.

Experiments are presently being run to increase the number of subject and the range of the study.


PULMONARY VENTILATION / SURFACE AREA (liters/min./m²)
20
15
10
5
0
0 1 2 3 4 5 6 7 8 9
TIME (minutes)

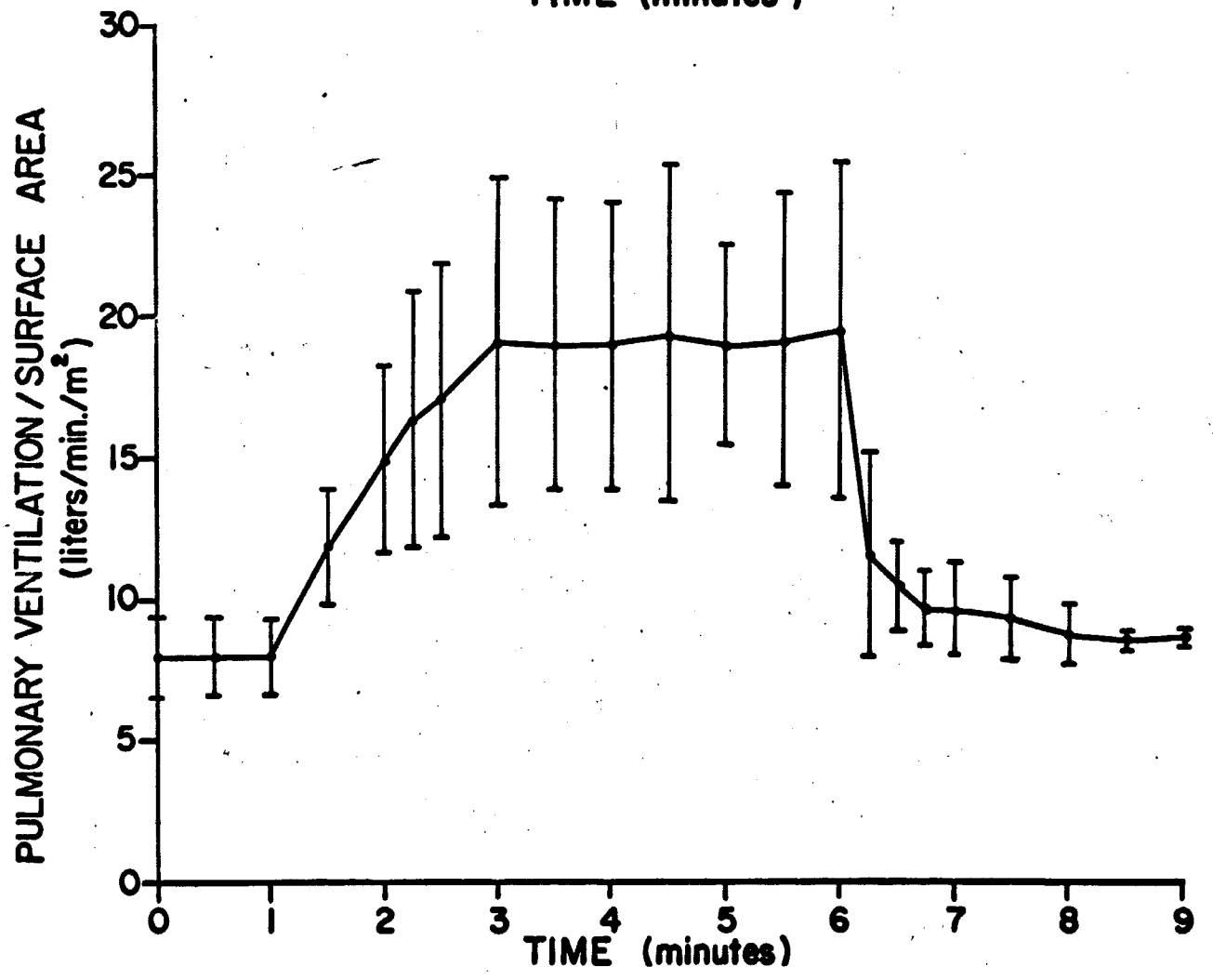

PULMONARY VENTILATION / SURFACE AREA (liters/min./m²)
30
25
20
15
10
5
0
0 1 2 3 4 5 6 7 8 9
TIME (minutes)

FIGURE 7

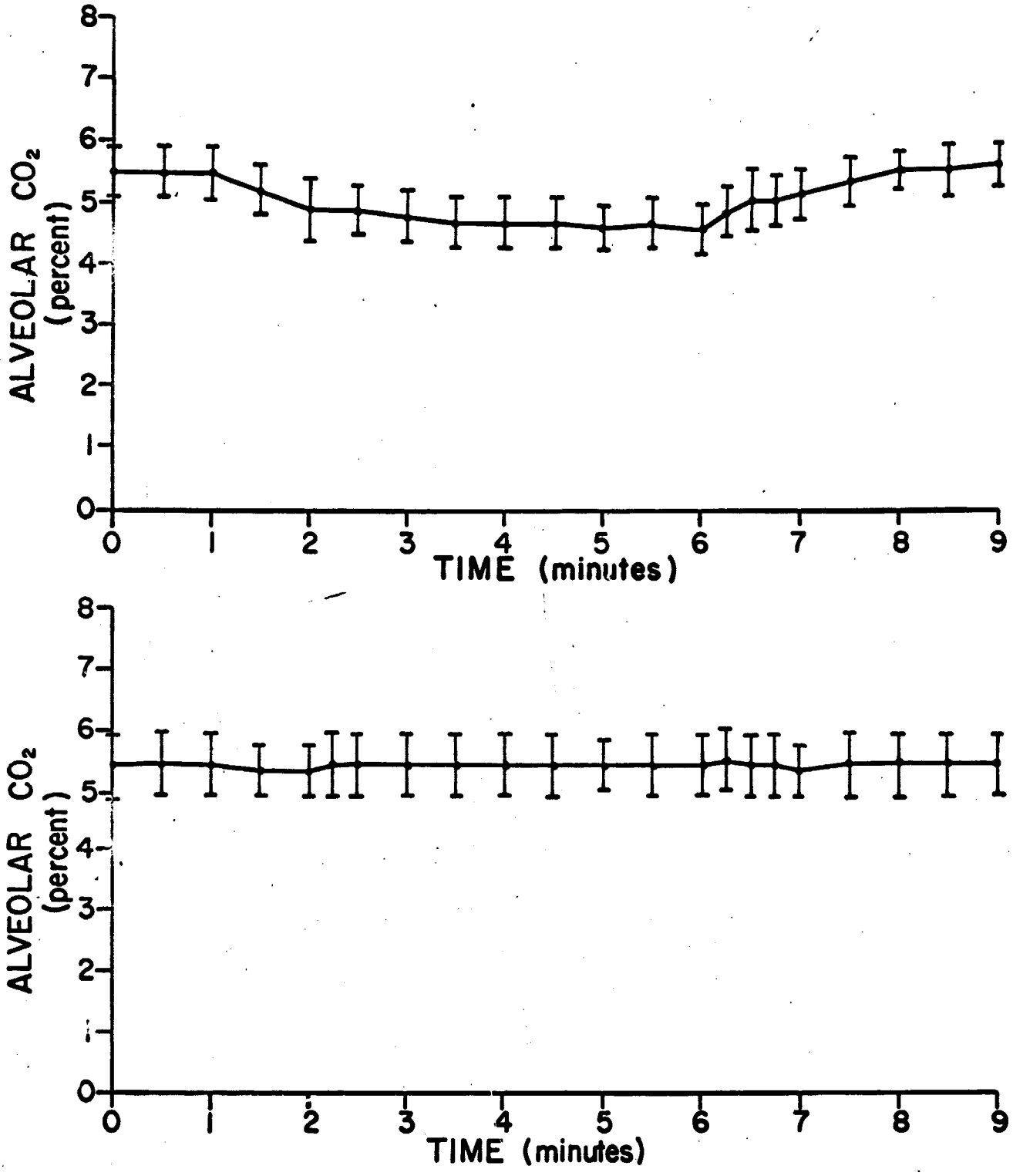
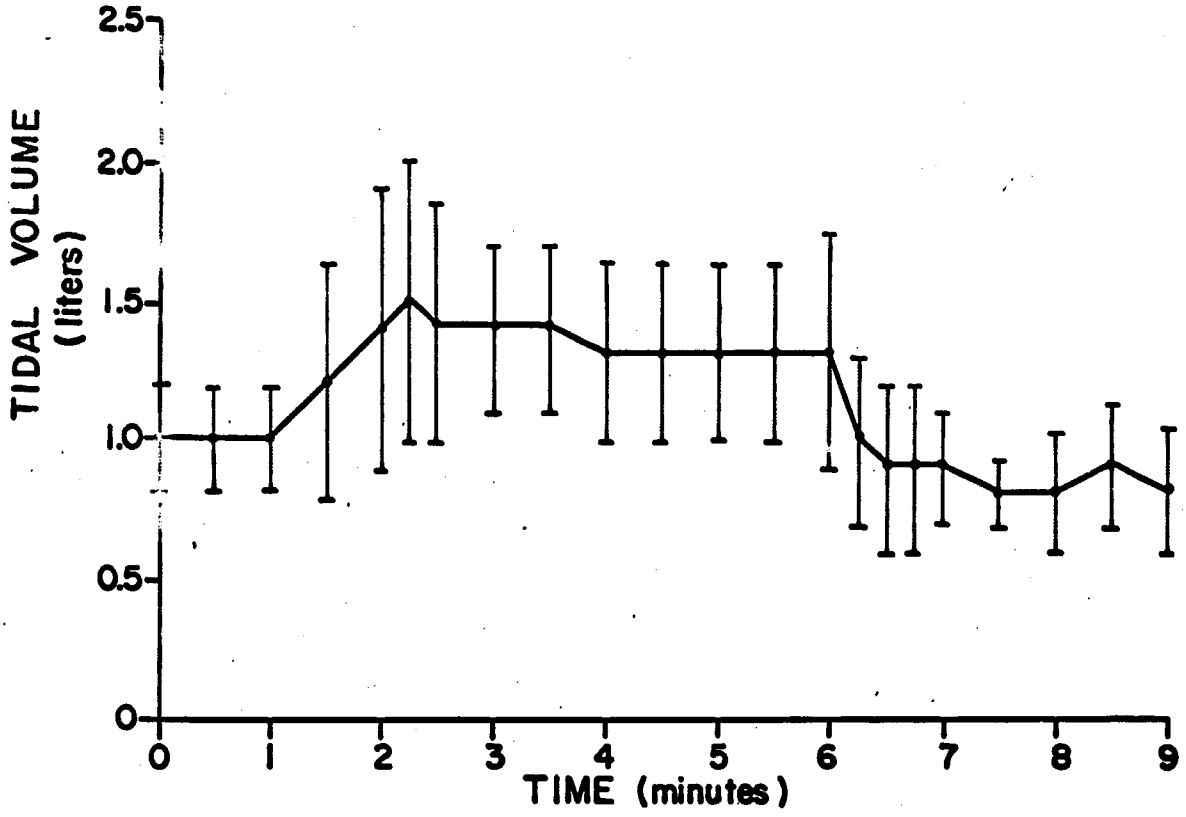

ALVEOLAR CO_2 (percent)
0
1
2
3
4
5
6
7
8
TIME (minutes)
0
1
2
3
4
5
6
7
8
9
ALVEOLAR CO_2 (percent)
0
1
2
3
4
5
6
7
8
TIME (minutes)
0
1
2
3
4
5
6
7
8
9

FIGURE 8


TIDAL VOLUME (liters)
2.5
2.0
1.5
1.0
0.5
0
0 1 2 3 4 5 6 7 8 9
TIME (minutes)

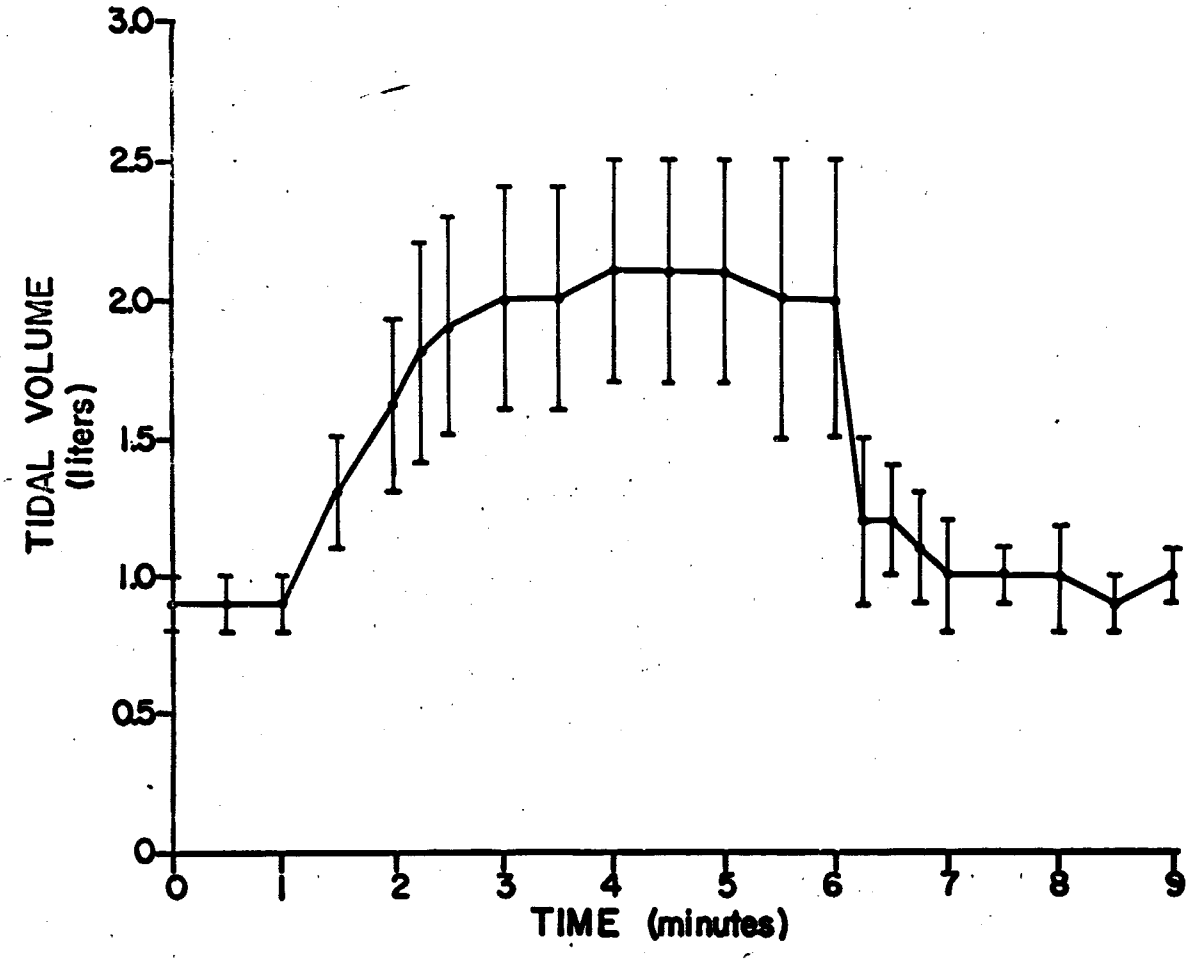

TIDAL VOLUME (liters)
3.0
2.5
2.0
1.5
1.0
0.5
0
0 1 2 3 4 5 6 7 8 9
TIME (minutes)

FIGURE 9

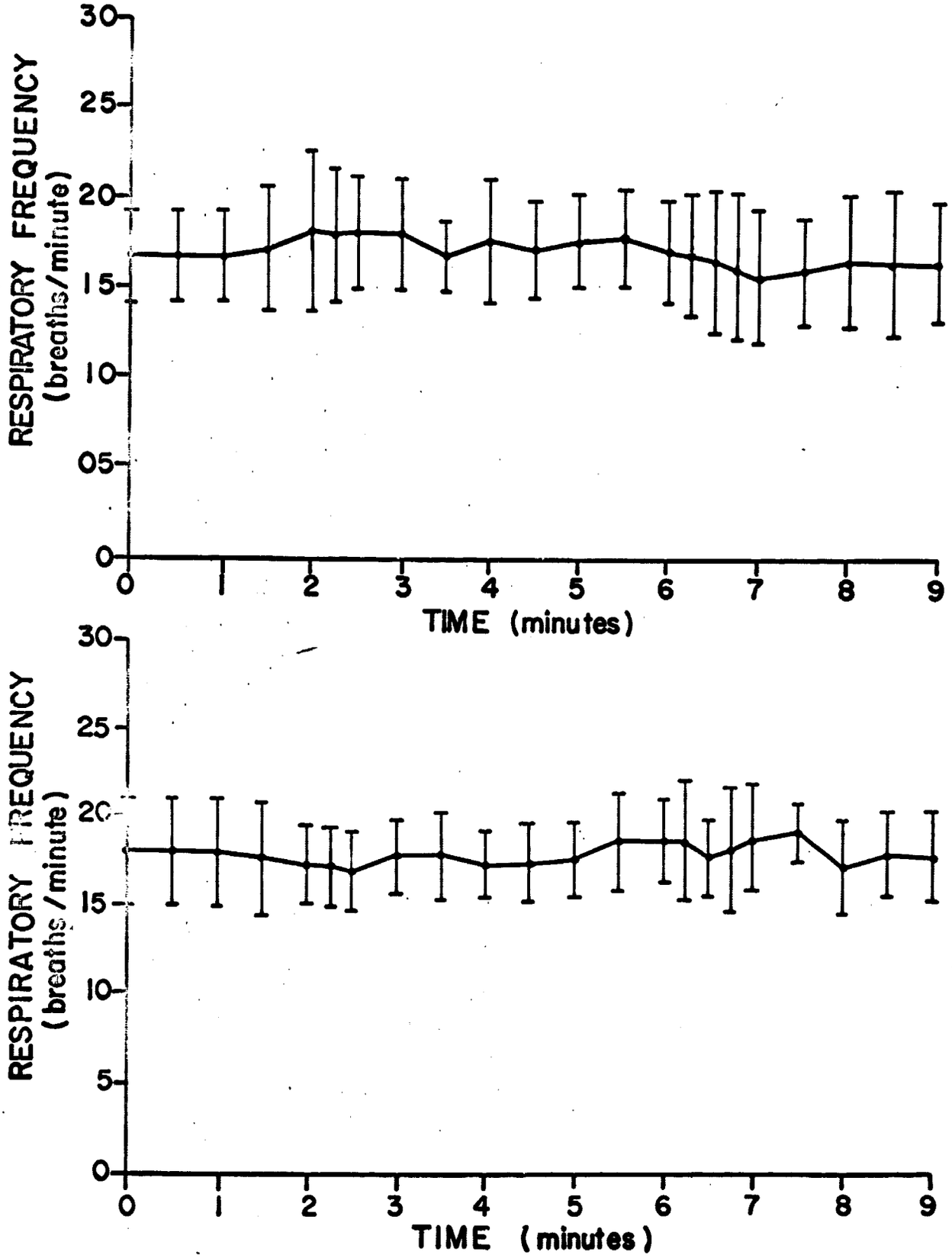

RESPIRATORY FREQUENCY
(breaths/minute)
30
25
20
15
10
05
0
0 1 2 3 4 5 6 7 8 9
TIME (minutes)
RESPIRATORY FREQUENCY
(breaths/minute)
30
25
20
15
10
5
0
0 1 2 3 4 5 6 7 8 9
TIME (minutes)

FIGURE 10

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