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FINAL TECHNICAL REPORT

Conceptual Idea of Digital Computer Model
of Human Respiratory System

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DIGITAL SIMULATION AND EXPERIMENTAL EVALUATION OF THE CO₂-H⁺ CONTROL OF PULMONARY VENTILATION

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Previous models of the CO₂-H⁺ control of ventilation have been concerned either with the response to CO₂ inhalation^{3,8} or the response to perfusion of the surface of the medulla with mock cerebrospinal fluid having a high Pco₂⁶. Simulation of both responses with the same model has not been attempted. The purpose of the present study was two fold; first to develop such a model and, second, to obtain experimental data from human subjects for both developing this model and for evaluating this and future models.

Experimental Data

By use of the black box approach to the human respiratory system, one can obtain a considerable amount of useful information. One possible view of the respiratory system as a black box is illustrated in Figure 1. The system inputs are the inspired concentrations of oxygen and carbon dioxide (F_{IO₂}, F_{ICO₂}) and the outputs are respiratory frequency (f), tidal volume (V_T), and alveolar oxygen and carbon dioxide partial pressures (P_{AO₂}, P_{ACO₂}). Minute ventilation (V) is computed secondarily from tidal volume and respiratory frequency. We will be concerned with the step responses to F_{ICO₂} only. Responses to sudden changes in F_{IO₂} with and without end-tidal Pco₂ controlled at normal levels have also been obtained by the authors, but since they do not directly pertain to the portion of the system described in this paper they will be omitted¹¹.

Subjects used were healthy males in their third decade of life. The instrumentation used is described in detail elsewhere by Holloman and Milhorn⁵ and is shown schematically in Figure 2. The input side of the apparatus consisted of a five-way valve through which the operator selected either room air or the stimulus mixture supplied from a 60-liter meteorological balloon, which was in turn supplied from a commercial compressed gas cylinder. The subject breathed through a mouthpiece connected to a respiratory valve system consisting of two Rudolph valves arranged in parallel. This arrangement was found to be the best compromise between low resistance and the desired low dead space. Expiratory flow was measured by a heated Fleisch pneumotachograph and Statham pressure transducer. The flow signal was detected by a trigger circuit which produced a short-duration pulse output at the end of each expiration. Gas was continuously sampled through needles inserted into the mouthpiece and was analyzed by a Beckman LB-1 infrared CO₂ analyzer and a Thermo fuel cell oxygen analyzer. The flow signal, the trigger pulses, and the continuous outputs of the oxygen and carbon dioxide analyzers were recorded on four channels of a magnetic tape using a Sanborn 3907 FM magnetic tape system. After an experimental session, the recorded data was played back, demodulated, digitized, and calculations performed by a Digital Equipment Corporation PDP-9 digital

computer. For each breath, the computing routine calculated the tidal volume by integration of the flow signal and the respiratory period by measuring the elapsed time between trigger pulses. From this, the respiratory frequency and minute ventilation associated with that breath were calculated. The highest carbon dioxide and lowest oxygen values occurring during the breath were also determined and stored as approximations of their alveolar concentrations. The occurrence of the pulse on the trigger channel was used by the program to initiate and terminate processing of input data for each breath.

After the calculations for the entire experimental run had been performed, the breath-by-breath values for tidal volume, respiratory frequency, minute ventilation, and alveolar oxygen and carbon dioxide were printed out and also stored as a data file on magnetic tape. The stored data could then be averaged into 10-sec intervals and displayed on a storage oscilloscope or plotted out by an on-line incremental drum plotter. All data files for a given stimulus concentration could also be accessed by another program and processed to give mean values and standard errors for each of the five variables.

Each experiment consisted of a 20-min prestimulus period breathing room air, a 25-min period breathing the stimulus mixture, and another 20-min off-transient period breathing room air. The stimulus mixtures were either 3, 5, 6, or 7 per cent carbon dioxide in air provided by commercial sources. The subjects were placed in a semirecumbent position in a comfortable recliner chair and listened to a stereophonic music through headphones. The music was provided both to relieve boredom and to mask out any ambient sounds occurring in the room during the course of the experiment. If necessary, instructions could be transmitted to the subject by the operator by use of an FM "wireless microphone" tuned to the frequency on which the music was being broadcast. All equipment was situated so that the subject could not observe the actions of the operator, the indication of any instrument, or the manipulation of any valve or control. Air from a compressed air tank was allowed to escape into the room during the periods when the stimulus mixture was not filling the reservoir bag so that the subject would not get an auditory cue when the stimulus was applied or removed. Subjects were not told which stimulus mixture they were to receive, and most underwent a "blank" experimental run in which compressed air was used in place of the CO₂ stimulus gas in order to detect the presence of voluntary effort, psychic efforts, etc., on the part of the subject.

The stimulus gas mixture was allowed to come to temperature equilibrium with the room air by passage through two series humidifier/heat exchangers and the reservoir balloon. Gas flow rates were kept low enough to prevent positive pressure from

developing in the balloon and to allow time for temperature equilibrium with the room air to be achieved. The degree of humidification provided by the humidifiers was such that subjects were unable to differentiate between room air and humidified compressed air from the reservoir balloon in several runs.

The experimental results for tidal volume, respiratory frequency, and minute ventilation are plotted in Figures 3-5. It can be seen from figures 3 and 4 that a characteristic dissociation of the frequency and tidal volume on-transients occurs at each stimulus concentration with tidal volume increasing rapidly to a stable plateau while the frequency rises very gradually throughout the stimulus period. Alveolar P_{CO_2} and P_{O_2} transients for all stimulus levels are given in Figure 6.

The steady-state values and transient half-times for the ventilatory variables are summarized in Table 1 and those for the gas pressures in Table 2. Several trends can be noted. The on-transient half-times for respiratory frequency steadily increase with increasing stimulus level while those for tidal volume increase in a nearly linear fashion. Ventilation on-transient half-times also steadily increase with increasing stimulus level. The on-transient half-times for alveolar P_{O_2} become progressively smaller as the stimulus level is increased. The half-times for the P_{CO_2} on-transients remain essentially constant until the 7 per cent level is reached. At this concentration the half-time becomes significantly larger. The off-transient half-times for respiratory frequency, tidal volume and minute ventilation all decrease with increasing stimulus concentration. Again it can be noted that the trend of the alveolar oxygen half-time is opposite to that of the other variables. The half-times for alveolar P_{CO_2} are essentially constant for all inspired CO_2 values. As the P_{CO_2} on-transients, the P_{CO_2} off-transients are the fastest ones observed. The off-transients for every variable except alveolar P_{O_2} are faster than the on-transient.

Computer Simulation

The model was divided into a controlled system and a controlling system. The former is illustrated in Figure 7. It consists of a lung compartment, a cerebrospinal fluid compartment, a peripheral sensor compartment, and a lumped tissue compartment. Arterial blood and venous blood were given their own CO_2 dissociation curves, and all tissues, for simplicity, were assumed to have the dissociation curve of brain tissue. In actuality, this is not a bad assumption when this curve is compared to those of the other major tissues. Cerebral blood flow was assumed to be a steady-state function of arterial P_{CO_2} and a first-order lag, as was the blood flow to the lumped tissue compartment. Blood flow to the peripheral sensor compartment was assumed to be constant. Cardiac output was then the sum of the individual flows. Circulation times were considered to be variable depending on the instantaneous flow rates.

The controlling system is shown in Figure 8. Ventilation is considered to be the sum of two components, a peripheral chemoreceptor component and a central chemoreceptor component. Each of these is determined by use of a function curve and a weighting function ($w=0.88$). The inputs to the two functions are assumed to be peripheral chemoreceptor hydrogen ion concentration (C_{pH+}) and central chemoreceptor hydrogen ion concentration (C_{csH+}). Alveolar ventilation (V_A) is determined from minute ventilation as follows: Tidal volume is computed from minute ventilation by use of a function curve based on data from the literature^{2,4,7}. Physiological deadspace (V_D) is then computed from tidal volume based on data from the literature¹. Minute ventilation is divided by tidal volume to obtain respiratory frequency. Respiratory frequency is then multiplied by deadspace to obtain minute deadspace ($\dot{V}_D$) which is subtracted from minute ventilation to give alveolar ventilation.

Viewing the central chemoreceptor as being located somewhere between cerebrospinal fluid and deep brain tissue, a P_{CO_2} gradient between cerebrospinal fluid P_{CO_2} ($P_{CSF_{CO_2}}$) and deep brain tissue P_{CO_2} can be described by

$$P_{CO_2} = P_{B_{CO_2}} + (P_{CSF_{CO_2}} - P_{B_{CO_2}}) \exp(-760 Q_{CS} X/D) \quad (1)$$

in which Q_{CS} is the blood flow in the neighborhood of the central sensor, S is the slope of the CO_2 dissociation curve, D is the diffusion coefficient of CO_2 , and X is the depth beneath the surface¹⁰. P_{CO_2} in this equation becomes the central receptor P_{CO_2} ($P_{CS_{CO_2}}$) at a value of X equals to its depth beneath the surface. The pH at this point is

$$pH_{CS} = 6.11 + \log \left[\frac{(C_{CS_{CO_2}} - \alpha_{CO_2} P_{CS_{CO_2}} / 760) / (\alpha_{CO_2} P_{CS_{CO_2}} / 760)}{1} \right] \quad (2)$$

and the hydrogen ion concentration is

$$C_{csH+} = \exp(-2.303 pH_{CS}) \quad (3)$$

The sensor depth is determined as shown in Figure 9. The solid lines were obtained from the model by fixing the sensor depth a various values. The number associated with each curve is the sensor depth in microns. Zero microns represents the surface of the medulla and 1000 microns is approaching the deep brain tissue level. The dots are experimental data from 14 human subjects. As can be seen, the 280 micron transient falls in the neighborhood of the experimental data. The sensor depth was, therefore, fixed at this value in the model.

Figure 10 shows the simulation results for step inputs of 3, 5, 6, and 7 per cent CO_2 . Comparison of this figure to Figure 5 shows that, in general, agreement between experimental data and model is good at all concentrations of inspired CO_2 .

Figure 11 shows the response of the model to step perfusion of the "surface of the medulla" with mock cerebrospinal fluid high in CO_2 . Data

from human subjects, as might be expected, is not available for comparison. However, Mitchell *et al.*¹⁰ did perform a similar experiment in anesthetized cats (Figure 12). A qualitative comparison can, therefore, be made. As can be seen, the response of the model appears to be similar in form to the response of the anesthetized cat.

In addition, using responses of the model to both CO₂ inhalation and CSF perfusion, the controller relationships of previous models^{3,8} were compared to the present one. Although differences in responses to CO₂ inhalation did occur with each controller relationship, they were not greatly different. The responses to CSF perfusion, however, varied greatly, the present relationship giving the most satisfactory result.

The responses of the model were also similar for CO₂ inhalation when the single central sensor was replaced by one monitoring cerebrospinal fluid H⁺ concentration and contributing 23 per cent of the central ventilatory drive and another monitoring deep brain tissue H⁺ concentration and contributing 77 per cent of the central ventilatory drive. The responses to cerebrospinal fluid perfusion, however, were considerably different in each case.

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TABLE 1. Summary of steady-state values and half-times for minute ventilation, tidal volume, and respiratory frequency.

VARIABLE	F_{ICO_2}	PRESTIMULUS CONTROL	25-MINUTE VALUE	ON-TRANSIENT $t_{1/2}$ (seconds)	OFF-TRANSIENT $t_{1/2}$ (seconds)
Minute Ventilation (liters/min)	0.03	6.3	11.25	64	43
	0.05	5.7	17.40	93	24
	0.06	5.8	27.41	123	16
	0.07	6.0	41.44	135	12
Tidal Volume (liters)	0.03	0.61	0.97	62	50
	0.05	0.59	1.15	72	27
	0.06	0.58	1.53	75	23
	0.07	0.60	1.79	78	19
Respiratory Frequency (breaths/min)	0.03	11.0	13.1	*	*
	0.05	11.5	17.9	206	29
	0.06	11.8	21.0	210	24
	0.07	12.1	25.5	225	23

* Not sufficiently well-defined to measure transient half-times.

TABLE 2. Summary of steady-state values and half-times for alveolar P_{O_2} and P_{CO_2}

VARIABLE	F_{ICO_2}	PRESTIMULUS CONTROL	25-MINUTE VALUE	ON-TRANSIENT $t_{1/2}$ (seconds)	% OVERSHOOT	OFF-TRANSIENT $t_{1/2}$ (seconds)	% UNDERSHOOT
P_{AO_2} (mm Hg)	0.03	102.5	126.0	72	0	49	0
	0.05	102.0	131.8	64	0	57	0
	0.06	100.9	132.1	61	0	75	0
	0.07	102.8	144.0	45	0	84	0
P_{ACO_2} (mm Hg)	0.03	42.2	44.3	6.6	24	6.0	27
	0.05	43.6	47.5	6.0	20	4.9	54
	0.06	42.5	48.9	5.7	0	4.7	63
	0.07	43.1	56.2	13.0	0	6.0	72

Figure Captions

1. The respiratory system as a black box¹².
2. Data collection system¹².
3. Transient tidal volume responses to steps of 3, 5, 6, and 7 per cent CO₂ in inspired air¹².
4. Transient respiratory frequency responses to steps of 3, 5, 6, and 7 per cent CO₂ in inspired air¹².
5. Transient minute ventilation responses to steps of 3, 5, 6, and 7 per cent CO₂ in inspired air¹².
6. Transient responses of alveolar Pco₂ and Po₂ to steps of (a) 3%, (b) 5%, (c) 6%, and (d) 7% CO₂ in inspired air¹².
7. The controlled system⁹.
8. The controlling system⁹.
9. Determination of central receptor depth (see text for explanation)⁹.
10. Transient minute ventilation responses of the model to steps of 3, 5, 6, and 7 per cent CO₂ in inspired air⁹.
11. Transient tidal volume and alveolar Pco₂ responses of the model to a step of CO₂ in cerebrospinal fluid⁹.
12. Transient tidal volume and alveolar Pco₂ responses of an anesthetized cat to a step of CO₂ in cerebrospinal fluid¹⁰.

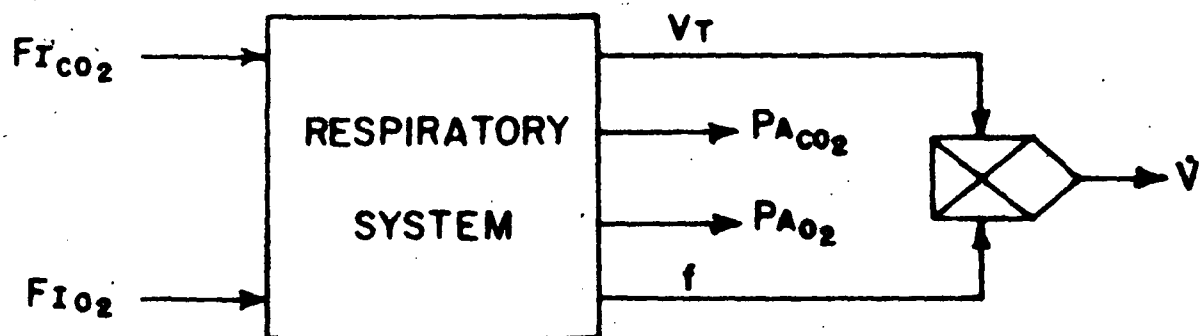


Figure 1

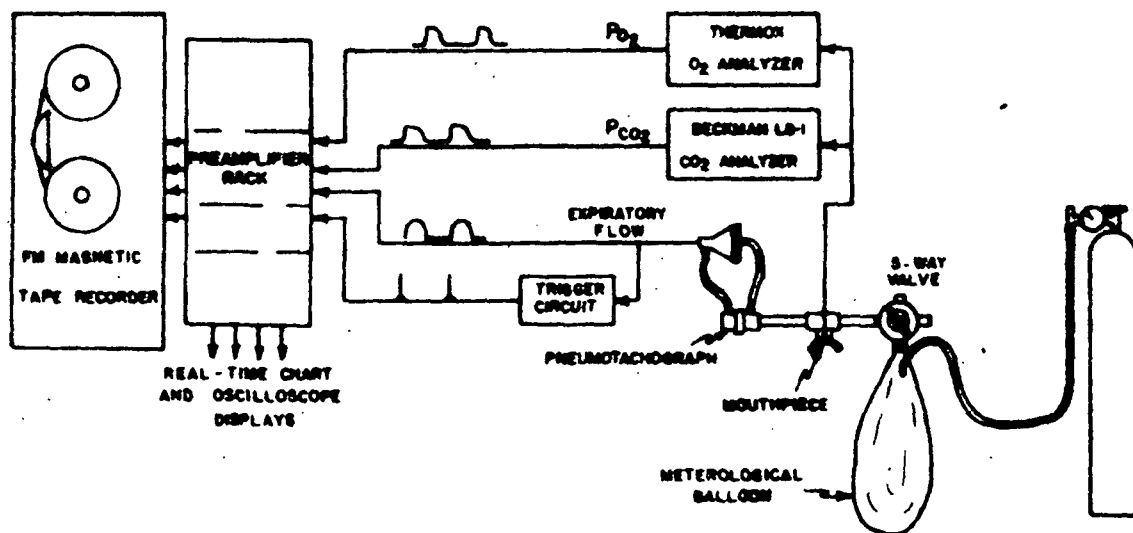


Figure 2

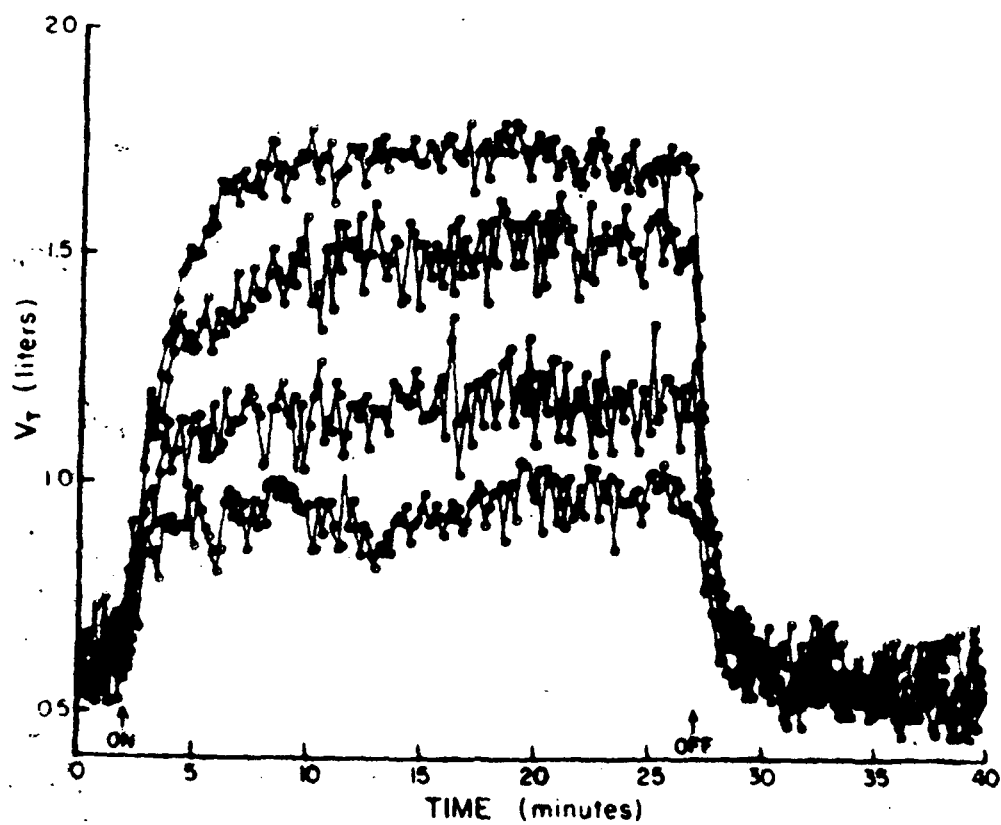


Figure 3

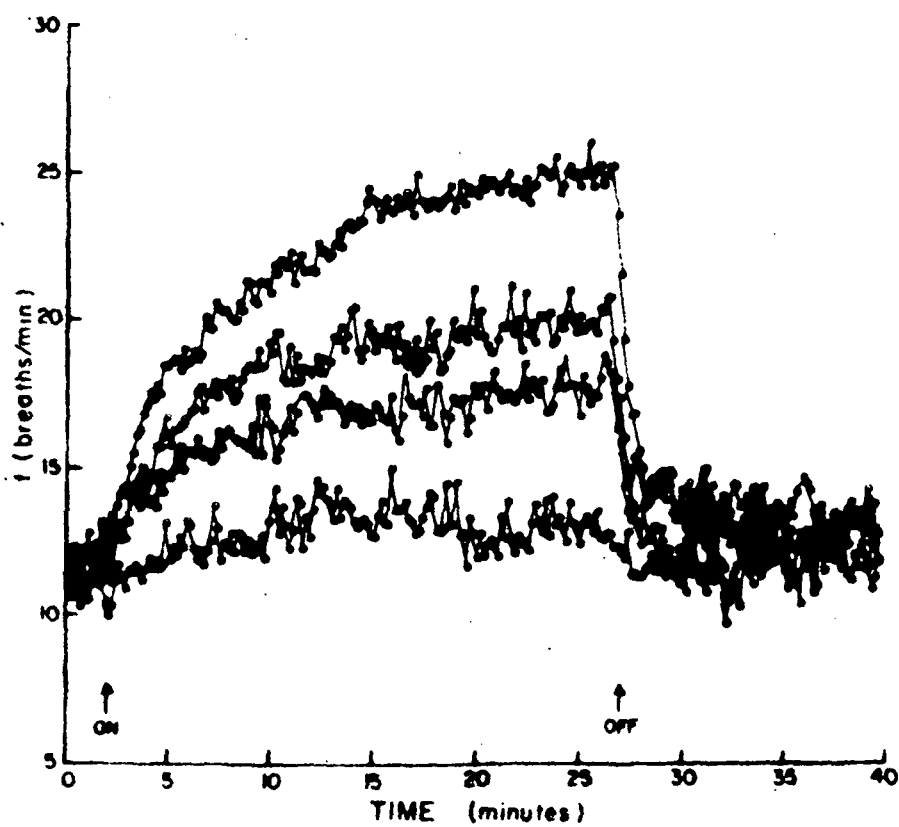


Figure 4

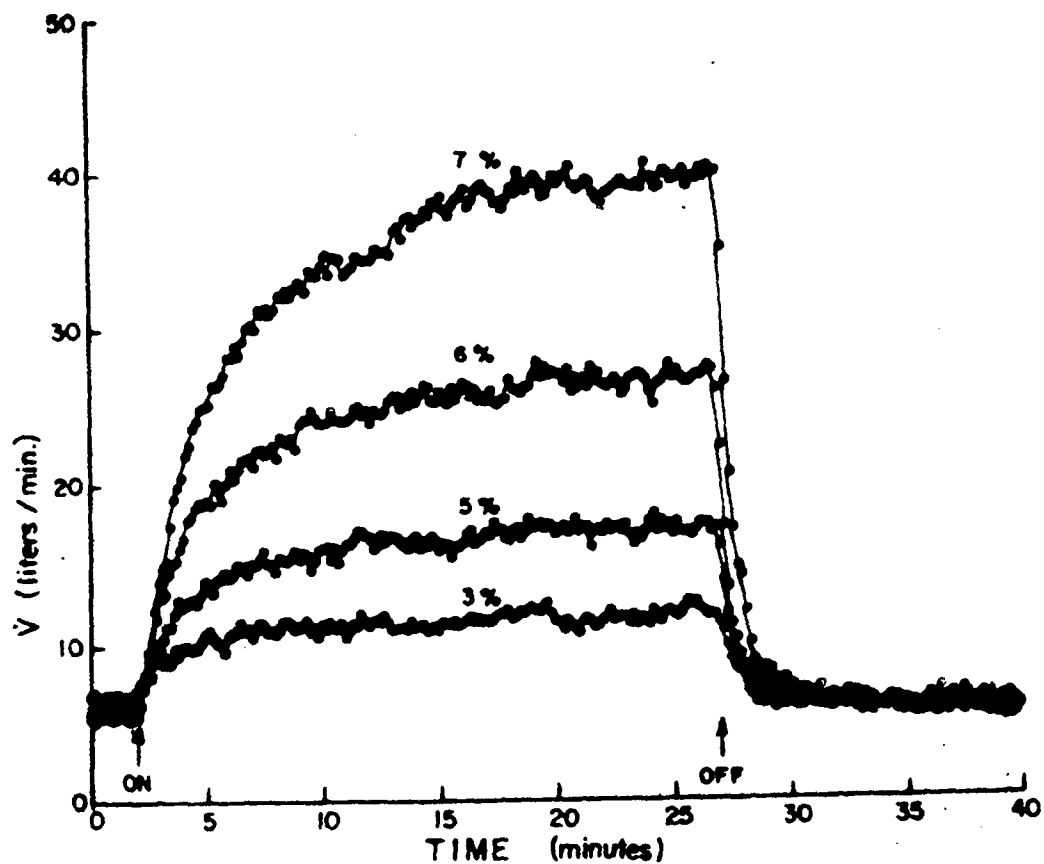


Figure 5

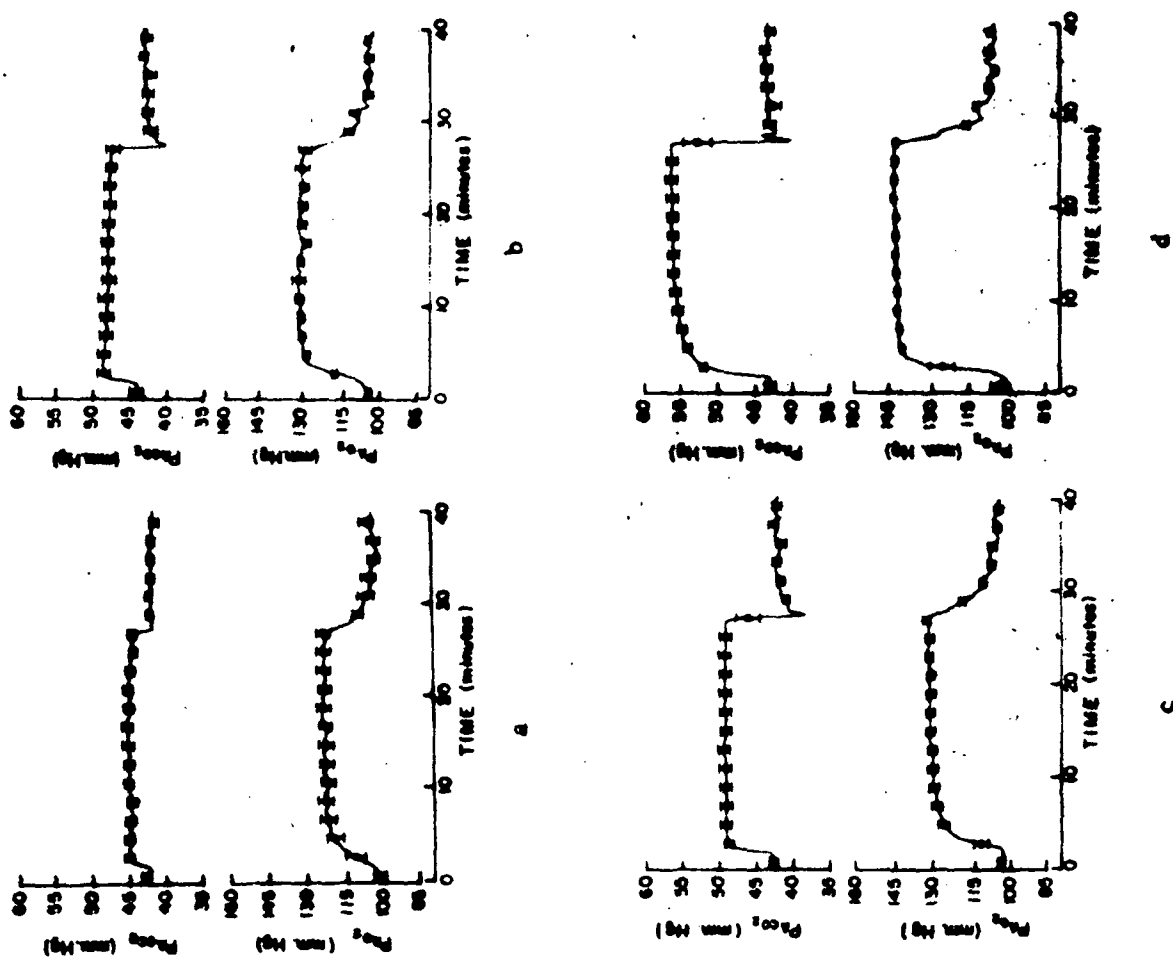


Figure 6

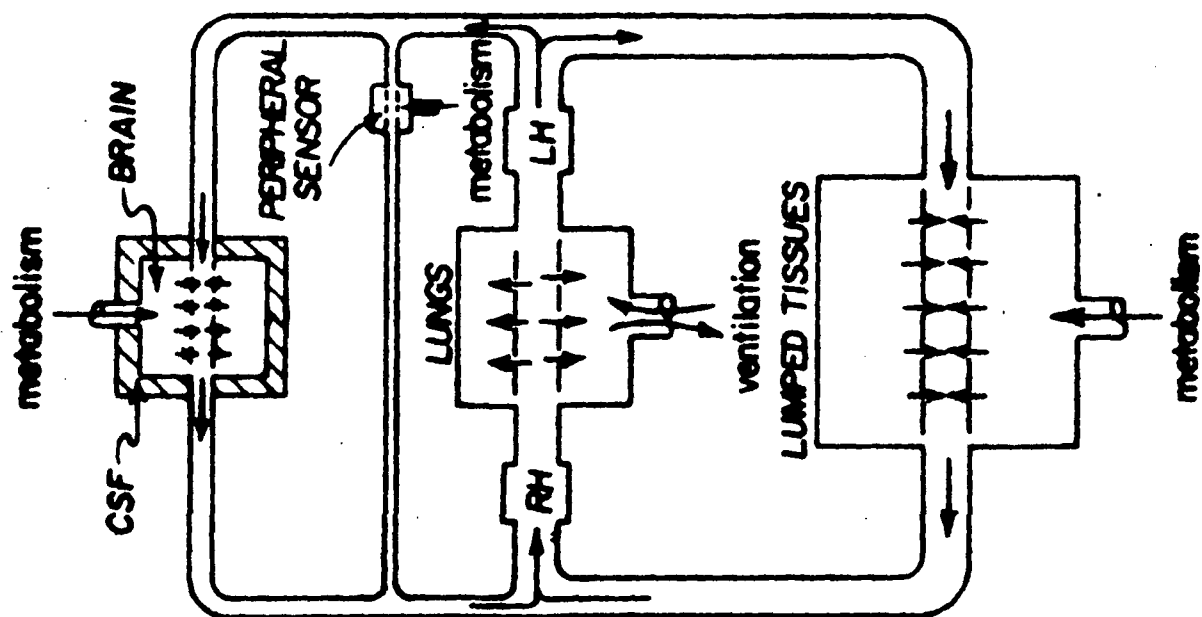


Figure 7

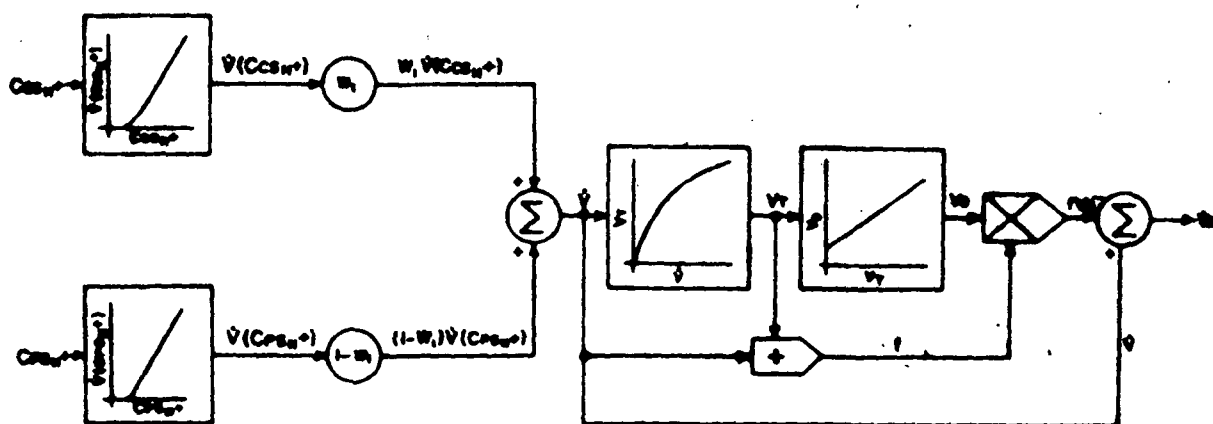


Figure 8

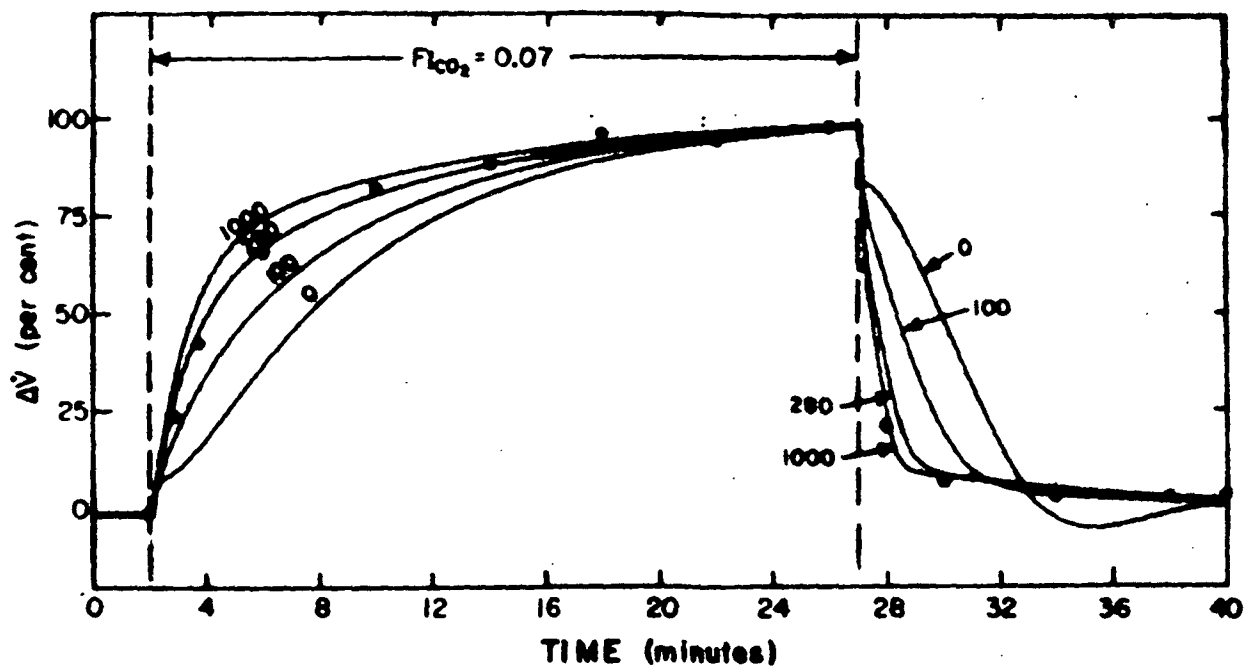


Figure 9

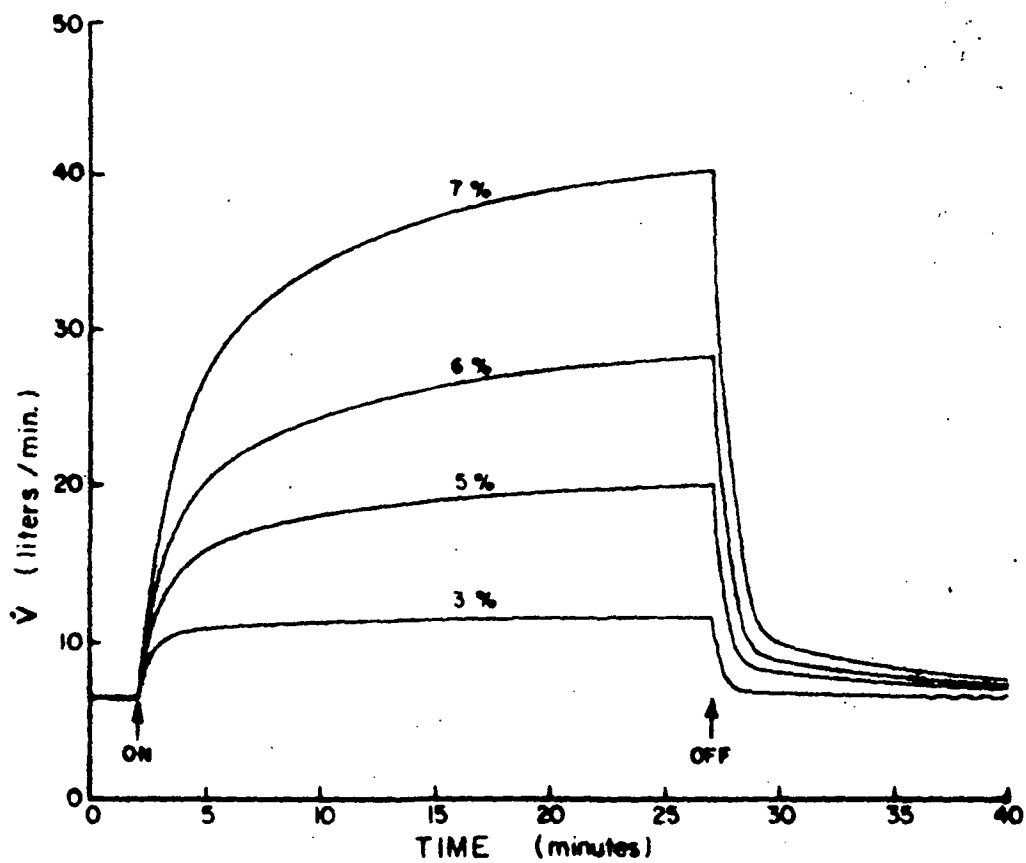


Figure 10

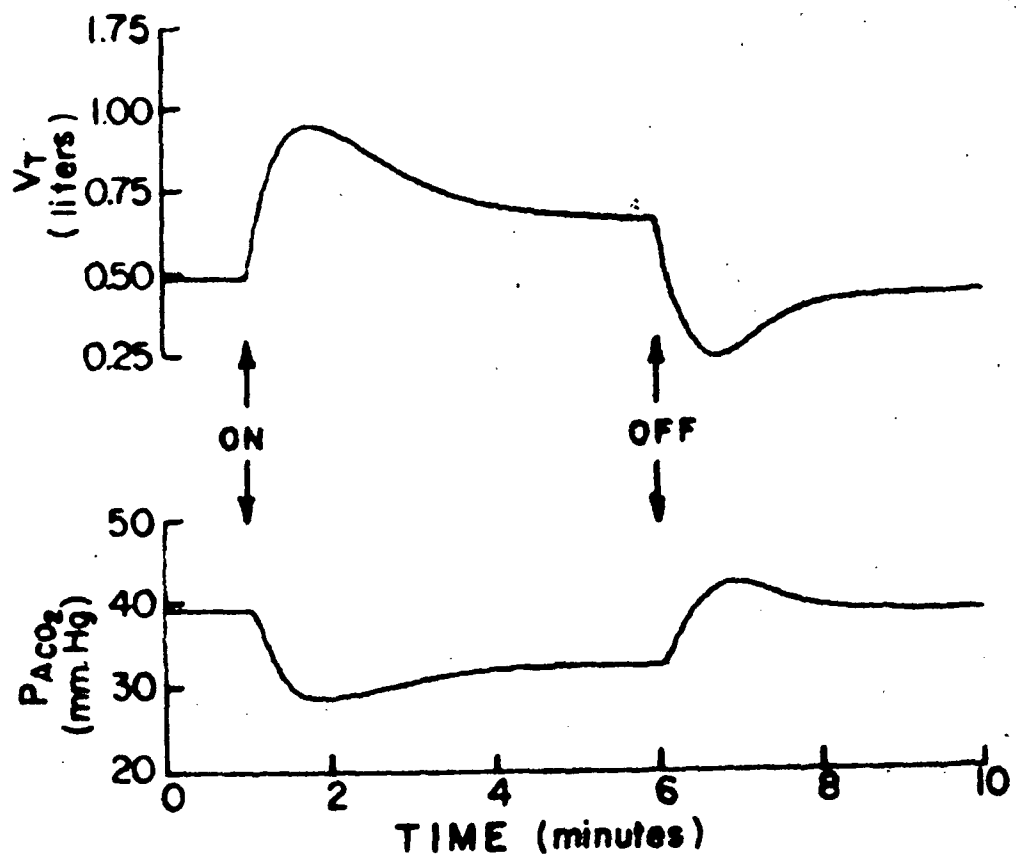


Figure 11

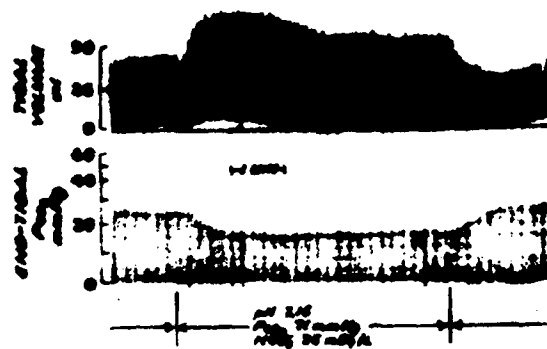


Figure 12