DIGITAL COMPUTER SIMULATION OF RESPIRATORY RESPONSE TO CEREBROSPINAL FLUID P_{CO_2} IN THE CAT

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ABSTRACT The respiratory control system is treated as linear with a transmission delay between ventilation and sensing points (chemoreceptors). To the accepted variables involving body gas stores, ventilatory effects, transmission effects, and steady state pH, P_{CO_2}, P_{O_2} chemoreceptor response, certain detailed analysis of the central receptors have been added. By construction of a model for medullary CO_2 receptor utilizing expected values of CNS (central nervous system) circulation, CO_2 production, and tissue-buffering effects, results of experimental observation of the effects of alteration of CSF were simulated. The inclusion of CSF effects also allowed simulation of the response to alteration in inspired CO_2, hyperventilation, and the periodic breathing with prolongation of circulation time.

The importance of CSF (cerebrospinal fluid) in the regulation of respiration was suggested by Leusen in 1950 (15) and further investigated by Loeschcke in 1958 (16). More recently the observation by Lambertsen (12) of the time course of the increase in ventilation induced by stepwise increase in inspired CO_2 and the rate of change of arterial and CSF pH, allowed an estimate of the relative contribution of CSF and arterial blood to ventilation as well as an indication of the time constants of the two controlling systems; a rapidly responding fraction of chemoreceptors reflecting blood gases and a more slowly changing fraction reflecting CSF. The net effect would be to reduce or damp the ventilatory response to transient changes in P_{ACO_2} (12). Mitchell, Loeschcke, Massion, and Severinghaus (17) improved upon earlier CSF perfusion studies and concluded that a sudden change in CSF P_{CO_2} is followed by a brief delay and that a change in ventilation occurs with a time constant of 20 seconds. These factors must be incorporated into any respiratory control system analysis especially when low frequency phenomena are simulated.

Simulation of the human respiratory system began with the work of Grodins (6), and was followed by that of Defares (3). Both models were reasonably successful in simulating ventilatory response to CO_2 inhalation, but could not simulate short-time

effects, such as those associated with periodic breathing. In their published work (7, 8) Horgan and Lange have presented the details of a model which does successfully simulate Cheyne-Stokes respiration. However, as this model was investigated further, two difficulties were encountered. In order to attain reasonable success in the simulation of CO_2 inhalation experiments, it was necessary to increase one of the time constants associated with the mixing of blood gases in the left heart from 10 to 20 seconds. On the other hand, recent experimental investigations indicate that this time constant should be much less than 10 seconds. These include the work of Lange (13, 14) in determining the effects of pulmonary artery to arterial passage from multiple indicator dilution curves, and the investigation of Charlton, Read, and Read (2) relating to the response of arterial blood gases to changes in alveolar gas.

Although the buffering effects of CSF have been recognized (11, 12, 15, and 16) these were not included in our earlier model. There, it was assumed that the activity of all of the chemoreceptors closely followed the changes in arterial blood. The work of Mitchell *et al.* (17) yielded information on the time course of ventilation following sudden changes in P_{CO_2} of cerebrospinal fluid. This allowed the inclusion of two additional storage compartments for CO_2—one representing the brain tissue, the other representing the cerebrospinal fluid. It is this improved model which is discussed in this paper.

METHODS

The basic ideas incorporated in the model are represented in the block diagram of Fig. 1. Except for the treatment of brain tissue and cerebrospinal fluid, the concepts are those described in detail in reference (8). Following the multiple factor theory of Gray (5), ventilation is taken to be proportional to the sum of factors dependent upon the P_{CO_2}, P_{O_2}, and pH of arterial blood. The pH does not appear explicitly in the diagram since it is assumed to depend on P_{CO_2} in the manner described by Gray. In the lung system block, equations based on conservation of CO_2 and O_2 describe a dynamic relationship between the input, ventilation, and the outputs, venous-arterial differences of both CO_2 and O_2 contents of blood. Equations describing the delay and mixing of the blood gases in the lung and left heart are based on knowledge obtained from indicator dilution measurements. To account for metabolism and the CO_2 and O_2 stores in the body, the equations used reflect the conservation of CO_2 and O_2 in two "storage" compartments.

In the previous model, both O_2 and CO_2 chemoreceptors were assumed to be affected only by the tensions in arterial blood. In the newer model, no change is made in the representation of the O_2 chemoreceptor, but the action of the CO_2 chemoreceptor is assumed to be modified by the buffering capacity of brain tissue and cerebrospinal fluid.

Fig. 2 illustrates the manner in which this model represents the relations between ventilation and the CO_2 tensions of arterial blood, brain tissue, and cerebrospinal fluid. The CO_2 chemoreceptors are considered to be distributed throughout a certain volume of brain tissue, including the areas on the ventrolateral surface of the medulla suggested by Mitchell *et al.* (17). This volume of tissue is perfused with blood, and its surface is considered in contact with cerebrospinal fluid. Accordingly, CO_2 can diffuse between blood and tissue, blood and CSF, and tissue and fluid.

Ideally, the concept set forth in Fig. 2 should be modeled as a distributed parameter

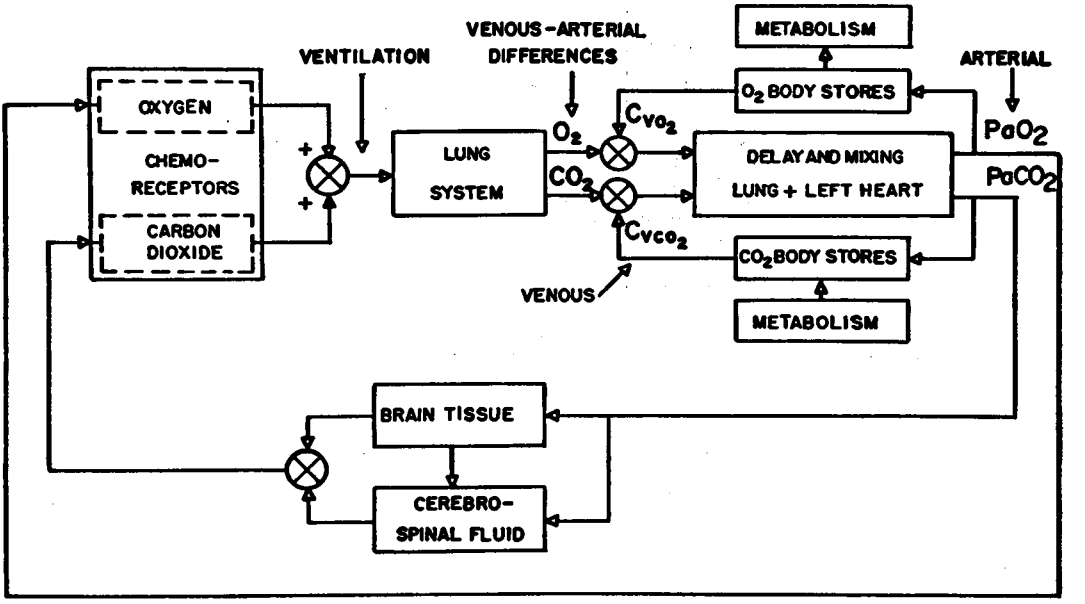

FIGURE 1 Block diagram of respiratory control system.

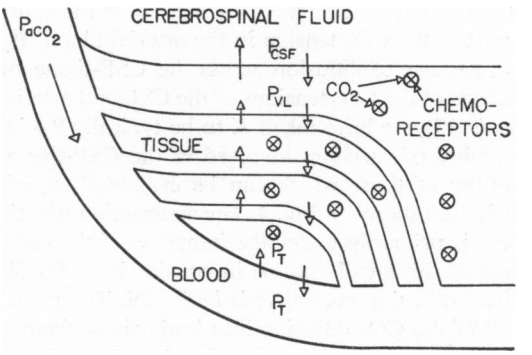

FIGURE 2 Schematic representation of the dependence of the action of CO_2 chemoreceptors on the CO_2 tensions of arterial blood, cerebrospinal fluid, and cerebral tissue.

system, because of the volume distribution of the perfusion, the metabolically produced CO_2, and the chemoreceptors. Such a detailed representation is not consistent with the rest of the simulation depicted in Fig. 1. In its place, the simplified, lumped parameter concept of Fig. 3 is used. In each of the three compartments which replace the distributed system, perfect mixing is postulated so that the tensions P_{CSF}, P_{VL}, and P_T are representative values for the three regions: CSF, ventrolateral surface, and brain tissue. Diffusion is assumed to take place at each barrier as indicated.

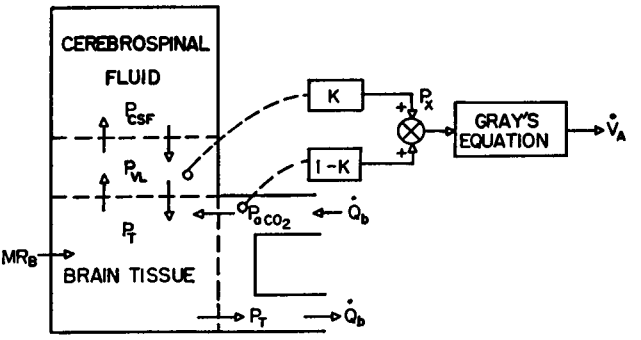

FIGURE 3 Three compartment representation of the distributed parameter system of Fig. 2.

The volume representing the ventrolateral surface (V_{VL}) is considered in close contact with the cerebrospinal fluid and, therefore, primarily under the influence of CSF. Thus, for the present purpose, it is reasonable to neglect the CO_2 exchange between arterial blood and this volume in comparison with the CO_2 exchange between arterial blood and the remaining tissue. Further, the influence of the CO_2 tension of the CSF is considered much greater than that of the CO_2 produced metabolically in V_{VL} because of the rapid diffusion into the CSF so that metabolically produced CO_2 is introduced only in the brain tissue compartment.

The distribution of the chemoreceptors is accounted for by assuming that the ventilatory drive is made up of 100 (K) per cent of the CO_2 tension at the ventrolateral surface, P_{VL}, and 100 ($1 - K$) per cent of the CO_2 tension in the arterial blood, P_{aCO_2}. Since P_{VL} is intimately related to P_{CSF}, because of diffusion across the CSF-tissue barrier, K and ($1 - K$) represent the relative effects of the CO_2 tensions of the CSF and arterial blood on ventilation. Following Mitchell *et al.* (17), we have taken K to be typically 0.4 in the cat.

In order that the number of variables involved in the CSF-tissue model be reduced to correspond to the number of those which can be evaluated experimentally, the concept has been further simplified, as shown in Fig. 4. The assumption that the volume representing the ventrolateral surface is primarily under the influence of the cerebrospinal fluid, allows elimination of the effect of this small volume in considering CO_2 diffusion between blood and CSF. Thus the direct diffusion path, K_B, is indicated. The path, K_A, indicates that we have considered that all of the CO_2 diffusing into brain tissue from CSF is confined to the ventrolateral surface (because of the short diffusion length) and that a negligible amount continues on to the remaining tissue. For both paths, diffusion rate is assumed proportional to the differences of tensions across the barriers.

The relations diagrammed in Fig. 4 can be described with the set of equations developed in the Appendix. Using equations 9 through 12 as a guide, it is possible to construct the block diagram of Fig. 5. The three blocks in Fig. 5 involving the time constants T_T, T_{CSF}, T_{VL}, represent exponential type time lags. For example, if P_{aCO_2} suddenly increases in a step fashion, P_T will rise exponentially with a time constant of, T_T seconds. If P_{CSF} suddenly increases, P_{VL} will rise exponentially with a time constant of T_{VL} seconds. Typical values are, T_T = 80 seconds, T_{CSF} = 220 seconds, and T_{VL} = 40 seconds.

As shown in the Appendix, the brain tissue time constant, T_T, is equal to $K_T/(Q_{\dot{B}}.E)$. K_T, the slope of the CO_2 dissociation curve for brain tissue, is taken as 0.36 volume per cent/mm Hg, the value given in reference (9) for dog brain: E, the corresponding slope

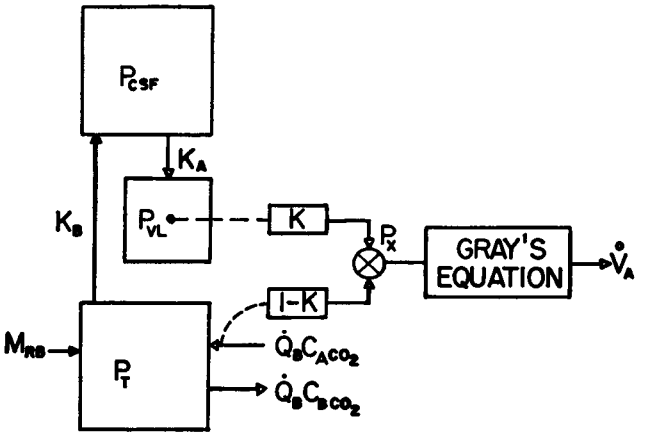

FIGURE 4 Simplified schematic representation of the three compartment model of Fig. 3.

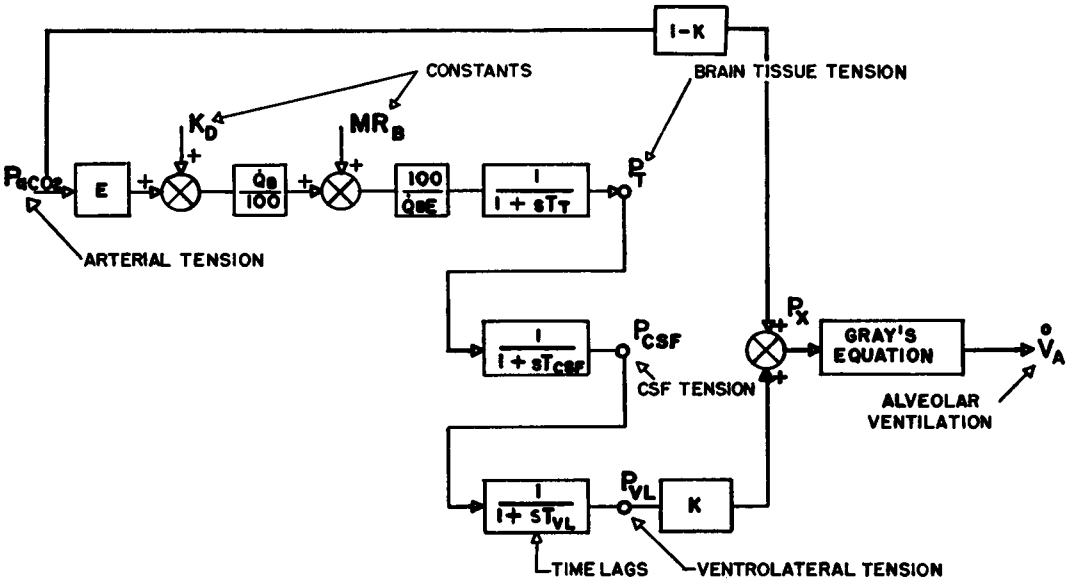

FIGURE 5 Block diagram of the equations used to represent the dependence of ventilation on the CO_2 tensions of arterial blood, cerebrospinal fluid, and cerebral tissue.

for blood, is taken as 0.45 volume per cent/mm Hg. $Q_{\dot{B}}$, cerebral blood flow, is taken 0.6 ml/minute per ml of brain tissue (10, 11). Thus, T_T = 1.33 minutes = 80 seconds.

When arterial P_{CO_2} is suddenly raised, the P_{CO_2} in the cerebrospinal fluid lags behind with a time constant of about 5 minutes (17). In the block diagram of Fig. 5, this time lag of 300 seconds between arterial blood and CSF is represented by the cascade combination of T_T and T_{CSF}. Since T_T is taken as 80 seconds, T_{CSF} is taken to be 200 seconds.

The time constant, T_{VL}, is that associated with the response of ventilation to sudden changes in the CO_2 tension of cerebrospinal fluid. Mitchell *et al.* (17) indicate that ventilation stabilizes at an increased level in about 60 seconds in response to sudden change in P_{CSF}. If we assume stabilization in three time constants, this implies a time constant of 20 seconds. It should be remembered, however, that when P_{CSF} suddenly increases, ventilation "heads for" a high value because compensation through arterial chemoreceptors has not yet come into play. In order to stabilize at the compensated level with a 20 second time constant, it is necessary to "head for" the higher, uncompensated value with a longer time constant. For the cat, this longer time constant is about 40 seconds.

RESULTS

The equations represented by Figs. 1 and 5 have been programmed on the IBM 1620. A flow diagram is available upon request.

Important parameters, descriptive of the cat, were taken as follows:

T_T, brain tissue time constant	80 seconds
T_{CSF}, CSF time constant (17)	220 seconds
T_{VL}, ventrolateral surface time constant (17)	40 seconds
T_C, appearance time, pulmonary artery to femoral artery (17)	3 seconds
T_1, T_2, time constants associated with mixing in lung and left heart (13, 14)	1 second 2 seconds
T_{EFF}, CO_2 body stores time constant (7, 8)	150 seconds
K, fractional effect of CSF on ventilation (17)	0.4
V_R, resting alveolar ventilation (1)	265 ml/minute
AV_{CO_2}, normal arterial-venous CO_2 content difference	4 volume per cent
P_{aCO_2}, normal arterial CO_2 tension	30 mm Hg
P_{VCO_2}, normal venous CO_2 tension	34 mm Hg
C_{aCO_2}, normal arterial CO_2 content	40 volume per cent
R. Q., respiratory quotient	0.8
$\dot{Q}_B$, cerebral blood flow (10, 11)	70 ml/minute
FRC, function residual capacity	150 ml

With these values, the experiment of Mitchell *et al.* (17) was simulated. In this experiment, the CO_2 tension of cerebrospinal fluid, P_{CSF}, was increased in steps. The experimental results, (Fig. 6*a*) show the effect on tidal volume and expired P_{CO_2} of sudden changes in P_{CSF}. Beginning with its normal value, P_{CSF} was suddenly increased by 20 mm Hg and held at this value for about 5 minutes. This was followed by another increase of 20 mm Hg for 5 minutes, and then a decrease of 20 mm Hg. Fig. 6*b* shows the computer results of running the same experiment on the model of Figs. 1 and 5.

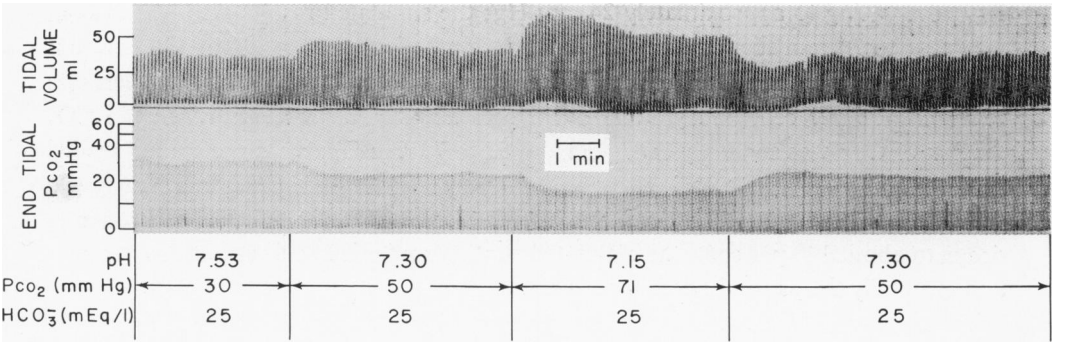

FIGURE 6*a*

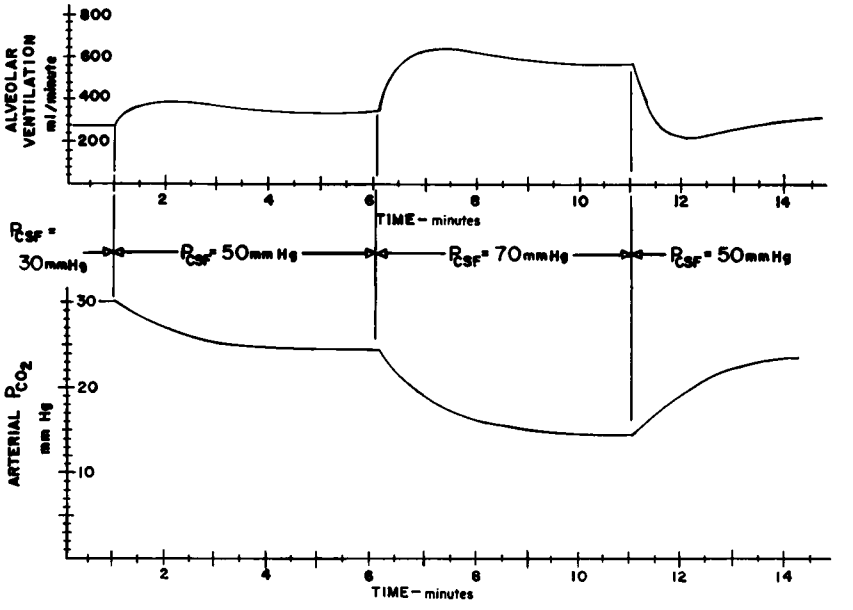

FIGURE 6*b*

FIGURE 6 (*a*) Experimental results of Mitchell *et al.* showing the effect of suddenly changing P_{CSF}, the CO_2 tension of mock cerebrospinal fluid of a cat. [Fig. 6*a* is from *J. Appl. Physiol.*, 1963, **18,** 528, Fig. 5, (courtesy of authors, reference (17) and *Journal of Applied Physiology*)]. (*b*) Simulated results, showing the effect in the model, of suddenly changing the CO_2 tension of cerebrospinal fluid in the same manner as in the experiment of Fig. 6*a*.

DISCUSSION

The agreement between results from the simulated respiratory system of the cat and the actual experimental results are good. When the CO_2 tension of CSF was suddenly changed from 30 to 50 mm Hg, the experimental results show end tidal

P_{CO_2} decreasing to approximately 24 mm Hg; the simulated results also show P_{aCO_2} dropping to 24 mm Hg. The measured tidal volume increases to about 140 per cent and then gradually drops to about 130 per cent. The simulated ventilation increases to about 150 per cent and gradually drops to about 120 per cent. When the CO_2 tension of CSF was suddenly changed from 50 to 70 mm Hg, the experimental results show end tidal P_{CO_2} decreasing to about 15 mm Hg; the simulated P_{aCO_2} drops to 15 mm Hg. The recorded tidal volume increases to about 200 per cent and gradually drops to about 140 per cent, the simulated ventilation increases to about 225 per cent and gradually drops to about 200 per cent.

The measured time constant for changes in end tidal P_{CO_2} is about 40 seconds; the comparable simulated time constant is about 60 seconds. The time to reach peak ventilation after each change is about 60 seconds, in both experimental and simulated results. This simulation follows earlier, less precise models in which the steady state chemoreceptor response was used and an alveolar to arterial transfer function which did not survive careful scrutiny. That a mathematical model successfully simulates a given response does not allow the conclusions that the model accurately portrays the prototype.

Our approach has incorporated increasingly refined simulation of parameters derived from independent observation and experimentation. Further, the simulation has progressed from a general identification of parameters which are critical to the stability or instability of the system (7) to the integrated effects of blood gases and hydrogen ion concentration (8) and finally includes precise portrayal of circulatory transfer function and dynamic response of the medullary receptors.

It should be emphasized that this simulation does not account for the effects of volume distribution in any part of the system, including the brain tissue, and, therefore, provides no information concerning the precise location of any functional entity, such as the chemoreceptors. Pappenheimer (18) has recently provided evidence relating to the location of the chemoreceptors.

At each stage of sophistication the adequacy of the model is checked by the successful simulation of the Douglas-Haldane experiment; hyperventilation followed by apnea and periodic breathing, the induction of periodic breathing by prolongation of circulation time (as observed in heart disease), and the response to increased CO_2 in the inspired air. Finally, the primary effects of isolated alteration of CSF have been predicted utilizing the present over-all model.

APPENDIX

Symbols Used.

AV_{CO_2};	arterial-venous CO_2 difference, volume per cent
Ca_{CO_2};	CO_2 content, arterial blood, volume per cent
CB_{CO_2};	CO_2 content, cerebral blood, volume per cent
C_{CSF};	CO_2 content, cerebrospinal fluid, volume per cent

C_T;	CO_2 content, cerebral tissue, volume per cent
C_{VL};	CO_2 content, ventrolateral surface, volume per cent
FRC;	functional residual capacity, milliliters
K;	fractional effect of CSF on ventilation
K_{CSF}, K_T, K_{VL}, E;	slopes of CO_2 dissociation curves, volume per cent/mm Hg
K_{CSFO}, K_{TO}, K_{VLO}, Ka_{CO_2}, K_{BCO_2};	intercepts of CO_2 dissociation curves, volume per cent
MR_B;	cerebral metabolic rate, ml CO_2/minute
Pa_{CO_2};	CO_2 tension, arterial blood, mm Hg
P_{CSF};	CO_2 tension, cerebrospinal fluid, mm Hg
P_T;	CO_2 tension, cerebral tissue, mm Hg
Pv_{CO_2};	CO_2 tension, venous blood, mm Hg
P_{VL};	CO_2 tension, ventrolateral surface, mm Hg
P_X;	CO_2 tension, effective for ventilation Hg
Q_B;	cerebral blood flow, ml/minute
$Q_{\dot{B}}$;	cerebral blood flow per unit volume, minutes^{-1}
RQ;	respiratory quotient
T_C;	appearance time, pulmonary to femoral artery, seconds
T_{CSF};	time constant, cerebrospinal fluid, seconds
T_{EFF};	time constant, CO_2 body stores, seconds
T_T;	time constant, cerebral tissue, seconds
T_{VL};	time constant, ventrolateral surface, seconds
T_1;	time constant, lung and left heart, seconds
T_2;	time constant, lung and left heart, seconds
V_R;	resting ventilation, ml/minute
V_{CSF};	effective volume, cerebrospinal fluid, ml
V_T;	effective volume, cerebral tissue, ml
V_{VL};	effective volume, ventrolateral surface, ml.

Equations Used. Applying conservation of the mass of CO_2 in each of the compartments of Fig. 4 results in the following three differential equations:

$$(V_{VL}/100)(d\,C_{VL}/dt) = K_A(P_{CSF} - P_{VL}) \quad (1)$$

$$(V_{CSF}/100)(d\,C_{CSF}/dt) = K_B(P_T - P_{CSF}) \quad (2)$$

$$(V_T/100)(d\,C_T/dt) = MR_B - (Q_B/100)(C_{BCO_2} - C_{aCO_2}) \quad (3)$$

These are to be solved, together with the equations describing CO_2 dissociation. These curves are assumed to be linear so that:

$$C_{VL} = K_{VL}(P_{VL}) + K_{VLO} \quad (4)$$

$$C_{CSF} = K_{CSF}(P_{CSF}) + K_{CSFO} \quad (5)$$

$$C_T = K_T(P_T) + K_{TO} \quad (6)$$

$$Ca_{CO_2} = E(Pa_{CO_2}) + Ka_{CO_2} \quad (7)$$

$$C_{BCO_2} = E(P_T) + K_{BCO_2} \quad (8)$$

When equations (4 through 8) are substituted in (1 through 3) and expressed as Laplace transforms then:

$$P_{VL}(s) = P_{CSF}(s)/(1 + T_{VL}s) \quad (9)$$

$$P_{CSF}(s) = P_T(s)/(1 + T_{CSF}s) \quad (10)$$

$$P_T(s) = 100/\dot{Q}_B E)[MR_B/s - (\dot{Q}_B/100)(K_D/s - EPa_{CO_2}(s)]/(1 + T_T s) \quad (11)$$

Where $T_T = K_T \cdot V_T/Q_B E = K_T/\dot{Q}_B E$.

$P_x(S)$ represents the driving CO_2 tension to be used in a form of Gray's equation:

$$V_A/V_R = 0.4P_x(S) - 14.6 \quad (12)$$

$P_x(S)$ reflects a portion of P_{VL} and a portion of P_T. Thus:

$$P_x(S) = KP_{VL}(S) + (1 - K)P_T(S) \quad (13)$$

Equations (9 through 12) are those diagrammed in Fig. 5.

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REFERENCES

1. ALTMAN, P. L., GIBSON, J. F., JR., and WANG, C. C., Handbook of Respiration, Philadelphia, W. B. Sanders Co., 1958.
2. CHARLTON, G., READ, D., and READ, J., Continuous intra-arterial PO_2 in normal man using a flexible micro-electrode, *J. Appl. Physiol.*, 1963, **18**, 1247.
3. DEFARES, J. G., DERKSEN, H. E., and DUYFF, J. W., Cerebral blood flow in the regulation of respiration, *Acta Physiol. et Pharmacol. Neerl.*, 1960, **9**, 327.
4. DOUGLAS, C. G., and HALDANE, J. S., The causes of periodic or Cheyne-Stokes breathing, *J. Physiol.*, 1909, **38**, 401.
5. GRAY, J. S., Pulmonary Ventilation and its Physiological Regulation, Springfield, Ill. Charles C Thomas, 1949.
6. GRODINS, F. S., GRAY, J. S., SCHROEDER, K. R., NORINS, A. L., and JONES, R. W., Respiratory responses to CO_2 inhalation. A theoretical study of non-linear biological regulation, *J. Appl. Physiol.*, 1954, **7**, 283.
7. HORGAN, J. D., and LANGE, R. L., Analog computer studies of periodic breathing, *IRE (Inst. Radio Engrs.), Trans. Bio-Med. Electron.*, 1962, **9**, 221.
8. HORGAN, J. D., and LANGE, R. L., Digital computer simulation of the human respiratory system, *Institute Electrical and Electronic Engineers International Convention Record*, 1963, **9**, 149.
9. KAZEMI, H., and MITHOEFER, J. C., CO_2 Dissociation curve of dog brain, *Am. J. Physiol.*, 1963, **205**, 598.
10. KETY, S. S., Measurement of local blood flow by the exchange of an inert, diffusible substance, *Methods Med. Res.*, 1960, **8**, 228.
11. LAMBERTSEN, C. J., and OWEN, S. G., Continuous, constant-rate sampling modification of nitrous oxide method for cerebral blood flow in man, *Methods Med. Res.*, 1960, **8**, 262.
12. LAMBERTSEN, C. J., SAMPLE, J. G., SMYTH, M. G., and GELFAND, R., H^+ and pCO_2 as chemical factors in respiratory and cerebral circulatory control, *J. Appl. Physiol.*, 1961, **16**, 473.
13. LANGE, R. L., and BOTTICELLI, J. T., Influence of venous injection sites on the evolution of dilution curves in dogs, *Am. J. Physiol.*, 1963, **205**, 504.
14. LANGE, R. L., HORGAN, J. D., BOTTICELLI, J. T., TSAGARIS, T. J., CARLISLE, R. P., and KUIDA, H., The transfer function of pulmonary to arterial circulatory passage and its relation to respiratory control, *J. Appl. Physiol.*, submitted for publication.

15. LEUSEN, I. R., Influence du pH du liquide cephalorochidien sur la respiration, *Experientia*, 1950, **6**, 272.
16. LOESCHCKE, H. H., KOEPCHEN, H. P., and GERTZ, K. H., Uber den einfluss von wasserstoffionen konzentration und CO_2—Druck im liquor cerebrospinalis auf die atmurg, *Arch. Ges. Physiol.*, 1958, **266**, 569.
17. MITCHELL, R. A., LOESCHCKE, H. H., MASSION, W. H., and SEVERINGHAUS, J. W., Respiratory responses mediated through superficial chemosensitive areas on the medulla, *J. Appl. Physiol.*, 1963, **18**, 523.
18. PAPPENHEIMER, J. R., FENCL, V., HEISEY, S. R., and HELD, D., Role of cerebral fluids in control of respiration as studied in unanesthetized goats, *Am. J. Physiol.*, 1965, **208**, 436.