DYNAMICS OF CHANGES IN CARBON DIOXIDE STORES

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THE variations in carbon dioxide content of the body have been repeatedly investigated. There are good reasons for this continued interest since this information has become necessary to the physiologist who must decide the CO_2 tolerance of man exposed to confined spaces in submarines or space vehicles. To what extent does man act as a CO_2 absorber? At what rate can he store his chief waste product, CO_2? At what rate can he lose the stores which he normally carries with him? What are the physiological limits of CO_2 store loss and CO_2 store gain? These are but a few of the questions yet to be answered.

While there are many approaches and problems which can be reviewed, our main objective is to discuss the factors which determine the speed of CO_2 store accumulation or depletion. A vast amount of data on this topic has accumulated, but the number of articles is less impressive than the divergent results.

In one of the first reports Adolph and associates [1] commented on their own findings by saying that they "did not feel confident that in 33 minutes saturation was completed." Many of the articles published since deal with procedures lasting only a few minutes, while others required several weeks. The results indicate that the CO_2 storage capacity of the whole body mass may vary from 0.3 to 11.6 ml. of CO_2 which can be stored per kilogram of body tissue for 1 mm. change in P_{CO_2} (ml./kg. body weight/mm. CO_2).

One attempt to describe the behavior of CO_2 store changes was presented earlier.[2] This model treated all the tissues as a single compartment, described the experimental data obtained in anesthetized dogs, and yielded results essentially similar to those obtained by others in cats.[3] More recently one of us [4] suggested that the discrepancies of CO_2 storage noted above must be associated with the equilibration period and that the dynamics of CO_2 store changes must consider the body as composed of various compartments each with its own CO_2 storage capacity and perfusion rate. Recent careful experiments [5] also indicate that CO_2 store changes in man do not fit the single compartment concept.

This review will describe a model, crude as it is, which may provide a reasonable description of the CO_2 storage process and will compare its behavior with experimental results in the literature. Any model system has its limitations; to recognize its weaknesses is paramount. Yet we believe that our model provides an explanation for the variance in experimental results. Above all, it has pointed out that equilibration following a change in CO_2 environment requires hours for completion, a period far beyond most of the previous studies.

Our model is an electronic analogue superior to our previous mechanical models because its behavior can be presented for solution to a computer.[6]

After comparing results of the analogue with existing physiological data, we have concluded that the analogue is a good representation of the problem, and we are justified in explaining the existing physiological data on the basis of our computer results. In view of the simplifying assumptions made, the quantitative results may be challenged, but we hope to point out the most critical physiological parameters in CO_2 retention or CO_2 loss.

A MODEL FOR CHANGES IN CARBON DIOXIDE STORES

Let us first consider the simplest model which will demonstrate changes in CO_2 stores. Here the whole body is considered as a common pool, where CO_2 is in physical solution and in chemical combination. The total amount is a function of CO_2 tension of the alveolar gas or of the arterial blood. Under steady state conditions the amount of CO_2 produced by the body is equal to that expired, indicating that CO_2 stores remain unaltered. When alveolar ventilation is changed, a new alveolar tension is reached and the body stores

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readjust at a different level, the new steady state. This re-equilibration of body stores will require an elevation in CO_2 content if the alveolar CO_2 tension has increased (hypoventilation). Since the additional CO_2 stored is part of the metabolic production, the expired CO_2 must be reduced by an equal amount. Hyperventilation will cause opposite changes.

A mechanical model of this simplified description similar to the one previously described [2] is given in figure 1. A large reservoir represents the CO_2 content of body tissues, the flow of liquid into this reservoir is the CO_2 production and the outflow through a resistance, the CO_2 output through alveolar ventilation. The height of the liquid in the reservoir is the CO_2 pressure and the reservoir content represents the CO_2 body stores. When the system is left undisturbed for a sufficient time the liquid level will stabilize at a height at which the hydrostatic pressure in the reservoir will force an amount equal to the inflow through the outlet tube. Under these conditions the level in the reservoir will not change and a steady state will obtain. Variations in alveolar ventilation will be represented by a change in resistance to the outflow. If this resistance is decreased by half its value (equivalent to doubling the alveolar ventilation), the level of liquid will decrease. This will finally stabilize at half its original height, indicating that only half the pressure is necessary to drive the same liquid flow through the decreased resistance. During the equilibration period (the unsteady state) the outflow will be larger than

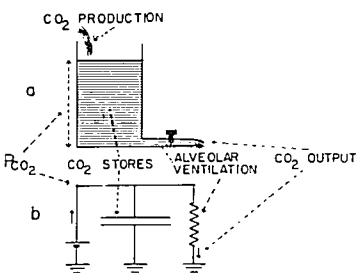

FIG. 1. A single compartment model for CO_2 stores of the body. The upper half represents the hydraulic model, and the lower half an electronic analogue. For details see text.

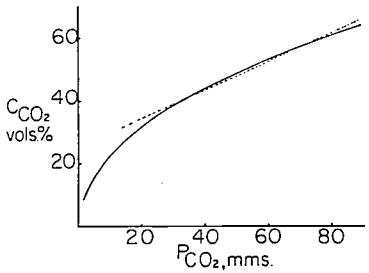

FIG. 2. The continuous line represents the CO_2 dissociation curve of blood. The dotted line is a straight line having a slope of .45 vol. per cent/mm. P_{CO_2}. The error introduced by assuming this to be the constant slope of the blood curve between 30 and 80 mm. P_{CO_2} is small compared to the variations in other biological parameters used.

during either initial or terminal steady state, the increment representing the decrease in content of the reservoir.

The changes which occur in the height of the reservoir (Δh) correspond to changes in CO_2 pressure (ΔP_{CO_2}), and changes in volume of the liquid (ΔV) are equivalent to changes in the CO_2 content of the stores (ΔC_{CO_2}). Therefore, both $\Delta C_{CO_2}/\Delta P_{CO_2}$ and $\Delta V/\Delta h$ (which represents the cross-sectional area of the reservoir) describe the slope of the dissociation curve of the CO_2 stores of the body. Only as long as the slope is constant (linear dissociation curve) the cross-sectional area of the reservoir is fixed. While we know that the dissociation curves of blood and tissues are not linear throughout, there is a tendency for linearity over a range of 30 to 80 mm. P_{CO_2} (fig. 2). In all our subsequent considerations we have assumed linearity in order to simplify our procedures.

With such a model, following a sudden change in outflow resistance (change in alveolar ventilation) the changes in CO_2 stores will be a simple exponential of time. When these changes are shown on a semilogarithmic plot as a fraction of the final change, versus time, a straight line is obtained. This type of behavior has been described in detail previously.[2]

An electrical analogue can also be designed and appears in figure 1 under the hydraulic model. This analogue is identical in its opera-

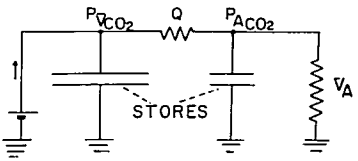

FIG. 3. An electronic analogue of CO_2 stores: the series model. In this the drop of CO_2 tension from tissues (assumed to be at mixed venous blood tension) to the alveoli is inversely related to the cardiac output. The drop in pressure between alveoli and atmosphere is inversely related to alveolar ventilation. Alveolar gas and arterial blood (right hand capacitance) are equilibrated at alveolar CO_2 tension, the rest of the body at mixed venous pressure tension.

tion to the hydraulic model. Its advantage lies in the fact that it can be more easily modified in a subsequent step to represent more faithfully the biological system. The CO_2 production of the body is now represented by the output of an electrical source (current intensity), the body compartments by a capacitor of capacitance C, and the alveolar ventilation by a resistance, R. The CO_2 tension is the potential. The total charge on the capacitor is the CO_2 store, while the capacitance is now the slope of the dissociation curve. Again, charge and potential will be altered by changes in resistance and the response to a stepwise change will be exponential. The time course of the change is best expressed by the time constant, which is the time necessary to produce $(e-1)/e$ (approximately 63 per cent) of the total content change. As an example, if the total change is 4 liters, the time constant is the time required to obtain a change of $.63 \times 4$ or 2.52 liters. In a linear system this time constant, T.C., is equal to $R \times C$.

Although either the hydraulic or the electronic model allows a description of the problem, they are inadequate for accurate estimation of changes. The models have assumed that the partial pressure of CO_2 with which the whole body has equilibrated is the alveolar tension. This is manifestly incorrect since a CO_2 gradient from tissues to alveolar gas is necessary in order to eliminate CO_2. To reproduce this in the model a double compartment has been described,[2] the assumption being made that the tension in mixed venous blood is a good estimate of the mean CO_2 tension of tissues. The bulk of the stores was assumed to be equilibrated at that particular tension, with only a minor fraction, representing arterial blood, equilibrated at P_{ACO_2}. The electrical analogue appears in figure 3.

Our model appears more complex than the one previously described only until the appropriate figures are considered. The pressure decline from tissue to alveoli is of the order of 6 mm., while the alveolar-atmospheric pressure difference is 40 mm., which is to say that the resistance added by introducing the circulation is small. Similarly, the fraction of stores equilibrated at alveolar pressure is only a minor one. The system should behave therefore very similarly to the single compartment system and under certain conditions has proved to discharge accordingly.[2]

The Multiple Compartment Model. In the single compartment system the change in vol-

TABLE I

STORAGE CAPACITY (SLOPE OF THE DISSOCIATION CURVE) OF THE BODY

Author and Reference	Species	Duration of Experiment, minutes	Slope, ml. kg. mm.
A. Mithoefer (4)	Man	1–5	.46
B. Klocke and Rahn (8)	Man	3–8	.40
C. Brocklehurst and Henderson (9)	Man	2–3	.50
D. Schaefer and Alvis (10)	Man	33	2.10
E. Lillehei and Balke (11)	Man	30	3.8
F. Vance and Fowler (5)	Man	20	1.30
G. Vance and Fowler (5)	Man	60	2.05
H. Farhi and Rahn (2)	Dog	30–45	1.50
I. Shaw (3)	Cat	30–90	1.60
J. Shaw and Messner (12)	Cat	100	1.80
K. Freeman and Fenn (13)	Rat	several weeks	up to 11.6

TABLE 2

CARBON DIOXIDE STORES OF THE BODY BY COMPARTMENTS

Electronic Equivalent	Weight, kg.	CO_2 Production, ml. min.	Blood Flow, ml. min.	Blood Flow, % of Total	Equil. Blood Volume, ml.	$(C_v - C_a)_{CO_2}$, ml. ml.	C_{CO_2}, ml. ml.	P_{CO_2}, mm.	CO_2 Content: Tissue, ml. kg.	CO_2 Content: Tissue, l. organ	CO_2 Content: Equil. Blood, liters	CO_2 Content: Total, liters	Slope of Dissociation Curve, ml. kg. min.	Slope of Dissociation Curve, ml. organ min.	Slope of Dissociation Curve, Equil. Blood Vol., ml. min.	Slope of Dissociation Curve, Total, ml. m.	Resistance, mm. ml. min.	Time Constant, min.
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
		Intensity						Potential				Charge				Capacitance	Resistance	Time Constant
Alveoli		240			2,400		.480	40		.160	1.15	1.31		1.0	10.8	11.8	.167	2.47
Heart	.30	26	210	4	180	.121	.601	67	187	.146	.109	.225	2.4	.7	.8	1.5	1.08	1.62
Brain	1.35	68	730	14	630	.093	.573	61	401	.542	.360	.902	2.9	3.9	2.8	6.7	.31	2.07
Muscle	28.0	40	850	16	720	.047	.527	50	342	9.600	.380	9.98	4.2	117.0	3.2	120.2	.25	30.0
Bone	2.2								12,300	113.0		113.0						
Fat	18.0								50	.900		.900						
Other	6.0	70	3,100	51	2,300	.023	.503	45	355	2.160	1.150	3.310	3.0	18.0	10.3	31.4	.10	1.98
Total	70	210	5,200	100	6,000					126.5	3.150	130.0*		165.2		174.6		

* If bone is excluded, the "total labile CO_2 store" (soft tissues) is 16.6 liters.

Columns (A), (C), and (D) were obtained from the Handbook of Biological Data.[13] Columns (B), (I), and (M) were obtained from Rahn.[4] Column (E) indicates the amount of blood equilibrated with a tissue or organ present in the venous circulation. It is assumed to be proportional to the perfusion of the organ and is calculated as 1,500 × (D). Column (F) is calculated as (B) ÷ (C). Column (G) is derived by adding (F) to .480 which is assumed to be the arterial blood CO_2 content. Column (H) is obtained by multiplying (F) by .0045 (which is assumed to be the slope of the blood dissociation curve), and adding the figure obtained to the arterial P_{CO_2}, assumed to be 40. Column J is calculated as (I) × (A). Column K is equal to (E) × (G) × $\frac{1}{1,000}$. Column L is the sum of (J) plus (K). Column N is derived by multiplying (M) × (A). Column O is .0045 × (E). Column P is the sum of (N) + (O). Column Q is $\frac{1}{.0045 \times (C)}$. Column R is (P) × (Q).

ume at any time is equal to P × cross-sectional area. Therefore, regardless of the duration of the experiment, the slope of the dissociation curve of the body should be identical. This is also approximately correct for the simple two-compartment system described.

Table 1 reviews the data appearing in the literature. There seems to be a gross relationship between duration of the experiment and slope of the dissociation curve of the body. The most significant data are probably those of Vance and Fowler on man.[5] These authors concluded that their results "demonstrate the different rates of exchange of alveolar gas, blood, and "tissues," and postulate that "there are probably multiple sites or pools with various rates of exchange." Rahn has also pointed out that there must be a wide variation between organs in terms of time course of CO_2 equilibration.[4] We decided therefore to modify the electronic model (fig. 3) by breaking down the main capacitance, that of the tissues, into separate components, each one being connected to the alveoli independently of others. With this in mind the various organs of the body have been tabulated separately (table 2). In this each major organ or tissue has been recognized as an individual equilibrating system, provided all the physiological parameters necessary were available. These included weight, CO_2 production, blood flow, CO_2 content, and the dissociation curve of this organ. From these data additional figures can be calculated. The electrical analogues are as before:

CO_2 production—current intensity
P_{CO_2}—potential
CO_2 content—charge
Slope of CO_2 dissociation curve—capacitance.

Since our computations, results and conclusions hinge on the values appearing in table 2, a critical discussion of these parameters appears in the appendix. We hope that in time more correct values may be obtained and substituted.

Two lines in the table are incomplete. The first one is bone. Although bone is the major CO_2 reservoir there is no agreement on whether or not the CO_2 content is related to P_{CO_2}.[12, 15] It is accepted, however, that these changes are limited, if they exist at all, in experiments lasting only a few hours. Body fat CO_2 changes have also been excluded from our final calculations. The amount of CO_2 dissolved in fat is far from negligible since α for animal fat is about 0.9 (nearly twice as large as for CO_2 in water).[15] However, fat is poorly perfused and cannot contribute much to changes in stores unless considerable time is available. If perfusion to body fat could be assessed, the adipose tissue could have been included in the computations. Thus, whereas the "total" CO_2 content (bottom of column) indicates the total CO_2 content for the whole body, "total" *changes* (sum of figures in column) are calculated to the exclusion of bone and fat, which are assumed to be so slow as to be negligible.

Resistance to CO_2 transport, the accepted ratio of pressure differential to flow, is calculated by using the difference between venous and arterial P_{CO_2} as ΔP, and the amount of CO_2 transported per unit time (which is the CO_2 production of the organ) as flow. This is also equal to the inverse of the product of organ flow times the slope of the CO_2 dissociation curve.

The product of the resistance and capacitance determines the time constant. It is this parameter which determines in the last analysis how effectively a compartment can use its storage capacity. This is obvious when we consider that regardless of the dissociation curve of an organ, the CO_2 discharged from the stores (as would occur in hyperventilation) must be discharged through the circulation. A low perfusion (indicated by a high resistance) may become the limiting factor in stores displacement. Conversely, when perfusion is high, the total capacitance of an organ can be brought into play rapidly. Muscle is the largest of all the capacitances involved (table 2). Because of this its time constant is extremely high, compared to other organs. Thus, electronically it became apparent that the properties of the system must be affected to a great extent by variations in the muscle system. Whenever resistance of the muscle compartment is decreased, a similar decrease in time constant will occur and the presence of muscle capacitance will be more effective.

The physiological reasoning is as follows: the muscle mass, representing 40 per cent of the body weight, is the largest buffering pool of all organs considered. It is therefore obvious that whenever the alveolar CO_2 tension will change, most of the changes in total body CO_2 (charge) content will be due to changes in muscle CO_2. However, it is also evident that unless blood flow to muscle is proportionate to its storage capacity, perfusion becomes the limiting factor. When this perfusion is low, changes in muscle CO_2 will be slow. If perfusion is increased, CO_2 can be moved more easily from or into the muscle. Blood flow to muscle was therefore one of the parameters we chose to alter, thus changing the time constant. An analogue designed according to values in table 2 was assembled with some modifications. The electronic characteristics of the computer used have been described by Spangler and Snell.[6] On this analogue we conducted three series of determinations, one with a muscle blood flow of 850 ml. minute, which is the basal flow [11]; a second one in which this was reduced to 25 per cent of this value, which might indicate what would be expected if blood flow to muscle decreased (shock, anesthesia); and a third one with a blood flow of muscle of 2500 ml. minute, which would be comparable to the result of moderate muscle activity.

In each series the following experiments were presented to the computer and compared with data from the literature: (a) hyperventilation, doubling the alveolar ventilation; (b) hypoventilation, decreasing alveolar ventilation to 50 per cent of initial value; (c) breath holding; (d) rebreathing in a 10-liter bag; (e) rebreathing in a 20-liter bag; (f) rebreathing in a 40-liter bag; (g) rebreathing in an 80-liter bag.

In each case the time changes in potential in the separate compartments were recorded.

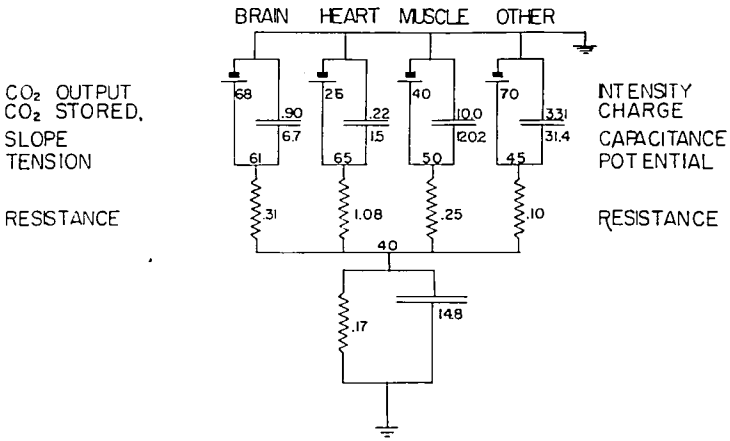

FIG. 4. Electronic model of CO_2 stores—multiple compartment analogue. This differs from the preceding model by the fact that the bulk of the body has been divided into separate compartments, all discharging in parallel into the alveolar space. The figures appearing in each compartment refer to the parameter appearing at the same height on the left (physiological terms) or at the right (electronic equivalent).

By multiplying the change in potential (partial pressure) by the slope of the "total CO_2 dissociation curve" of the compartment (capacitance), the changes in CO_2 content of the compartment (charge) could be calculated. Adding the changes in all the compartments at any given time gives the change in body CO_2 content at that instant.

RESULTS

Effects of Changes in Muscle Perfusion. Figure 5 shows the results of a fixed degree of hypoventilation under two of the conditions studied (*a*—basal perfusion to muscle; *b*—muscle perfusion decrease). In either case the alveolar ventilation has suddenly been reduced to one-half its normal value, the CO_2 production remaining constant. This will eventually double $P_{A_{CO_2}}$. In each half of the figure there are two curves. The continuous line represents the changes in $P_{A_{CO_2}}$, going from 40 to 80, while the dashed line represents the changes in stores.

The initial and final points are the same in the two halves of the figure. However, the time course of the events varies greatly. Under basal conditions there is a rise in P_{CO_2}, with slower changes in content. The right half of the figure shows gross deviations. The change in alveolar CO_2 is abrupt at first, and tails off with a slowly ascending plateau. This shape is typical of any record obtained when discharging a system in which two components with dissimilar time constants are set in paral-

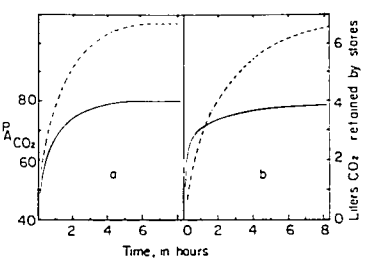

FIG. 5. Hypoventilation experiment. The left figure *a* describes the time course with basal blood flow to muscle. The right figure *b*, drawn at the same scale, shows the effects of reduced perfusion to muscle. In each figure the continuous line represents the $P_{A_{CO_2}}$ changes, and the dashed line, the stores CO_2 increase. For details see text.

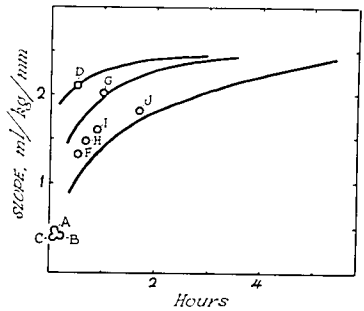

FIG. 6. Changes in slope of the body CO_2 dissociation curve with time. The middle line is the expected change with basal muscle perfusion, the one above it the expected change with increased muscle perfusion, and the lower one the changes with decreased muscle perfusion. Letters designate the experimental data from table 1.

lel. The first part represents essentially the fast component, while the second reflects the slow compartment. Relatively few readers may be familiar with "CO_2 washout curves" or "CO_2 wash-in curves" (as the ones presented). However, nitrogen washout curves are more customarily seen. They represent essentially the same situation. When all alveoli are similar in their properties a uniform washout curve is to be expected. When there are gross differences between various elements, the multicompartment curve with its initial rapid drop and subsequent plateau is encountered. This is what occurs to $P_{A_{CO_2}}$ when the time constant of the muscle mass is grossly disproportionate to that of the other elements. In this case the CO_2 content of the body (CO_2 retained by stores) rises at a slower rate than before. The discrepancy in time changes between the two parameters becomes evident.

The data reported in the literature are usually expressed in its final form as changes in CO_2 stores/kg. body weight/mm. $P_{A_{CO_2}}$. This information can be calculated from the curves appearing in figure 5. At any given time the change in stores CO_2 can be measured, divided by 70, to give the change per kilogram, and then divided again by the concomitant change in P_{CO_2}. A curve showing the change in calculated values versus time can be constructed from each of figures 5*a*, and 5*b*, as well as from hypoventilation with increased muscle perfusion. These curves are shown in figure 6, in which the "storage capacity" is plotted versus time. This figure shows that if our model is an adequate reflection of the experimental conditions, the storage capacity of the body should indeed vary with time. These variations are due to the lag in store changes versus alveolar CO_2 tension changes. A large resistance to blood flow in the muscle (decreased flow and large time constant) will increase this lag and therefore the time needed to obtain true equilibrium.

The letters appearing in figure 6 represent some of the data from table 1 and show that the discrepancies between experimental results can be explained by differences in equilibrating period and in muscle blood flow. It is interesting to note that points H, I and J pertain to animals anesthetized with barbiturates and are in agreement with a decreased blood flow to the muscle. On the other hand, the data on unanesthetized humans are compatible with a muscle blood flow equal to or higher than basal value.

Figure 6 has an even greater significance when analyzed in conjunction with figure 5. Alveolar ventilation is a calculated value; in physiological experiments there is no method which will produce an exactly predetermined change in alveolar ventilation; therefore the final $P_{A_{CO_2}}$ cannot be predicted. Thus the decision to assume that a new steady state has been achieved must be reached solely on the basis of the fact that the alveolar CO_2 tension remains steady. Figure 5 will show that at low blood flow to the muscle the CO_2 tension will tend to plateau early. This is obvious when we bear in mind that this is the condition in which CO_2 coming from muscle is just "trickling" to the alveoli and does not affect measurably the $P_{A_{CO_2}}$. As an example, if in an experiment the new steady state was defined *a priori* as the condition at which $P_{A_{CO_2}}$ varies by 1 mm. or less over a 15-minute period, experiment 5*a* would have been terminated at 135 minutes, while experiment 5*b* would have been stopped at 60 minutes, the respective storage capacities being 2.2 and 1.6 ml./kg./1 mm. P_{CO_2}.

Effect of Alveolar Ventilation. In the overall analysis CO_2 has to be carried from muscle

into as well as out of the alveoli. Thus alveolar ventilation will be a factor in determining the speed of equilibration of muscle CO_2 stores. In the analogue this is equivalent to describing the discharge of the muscle capacitance through two resistances in series. Thus the curves appearing in figure 5 pertain specifically to an alveolar ventilation of $\dot{V}_{CO_2}/40$. The effects of differences in alveolar ventilation have been computed but are too intricate for this review. The basic information is that the importance of alveolar ventilation varies inversely to muscle circulation, which is to say that when the limiting factor to CO_2 movement is mainly in muscle circulation, the total outflow resistance cannot be affected greatly by alveolar ventilation, which plays a small role.

Correlation with Existing Data. Before trying to apply to the living animal the conclusions derived from the analogue, it is necessary to show that when the latter is programmed to duplicate experimental conditions, the computer results are compatible with the physiological data.

The basic assumption made was that each segment of the body reacts to changes in CO_2 tension by varying its CO_2 content in the way an R-C system behaves. Bernimolin and others [17] have introduced $C^{11}O_2$ in the rectum of a dog between two ligatures and watched the elimination of labeled carbon dioxide through the lungs. When their data are plotted on a semilogarithmic scale, a rapid linear decrease is evident for the first 80 minutes. The slower phase appearing at that time is probably due to elimination from other body compartments which had retained $C^{11}O_2$ which had passer through the lungs. A similar record is obtained from the analogue when an additional charge is added to one of the capacitances.

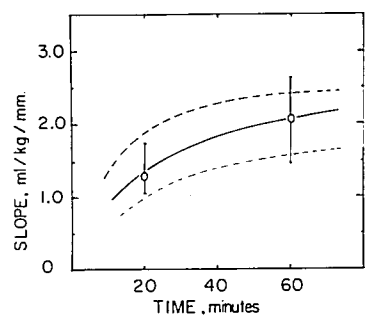

FIG. 7. Changes in slope of the CO_2 dissociation curve with hyperventilation. The continuous line is the expected change with basal muscle perfusion, the dashed lines the expected changes when muscle perfusion is increased (top) or decreased (bottom). The circles are the mean values obtained by Vance and Fowler in man and the vertical lines indicate the scatter in these values.

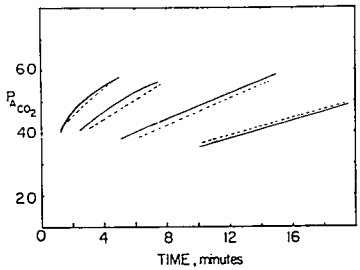

FIG. 8. Effect of rebreathing on alveolar P_{CO_2}. The continuous lines represent computer calculations, the dashed lines are the results of Mithoefer's experiments on man, rebreathing oxygen from a bag. The bag volume is 10 liters for the first pair of curves from the left, 20 for the second, 40 for the third, and 80 for the last.

Nichols [15] has studied equilibration of some of the body CO_2 stores in rats. The data for muscle CO_2 is essentially similar to that obtained on the computer and indicate that in the unanesthetized rat several hours are required for equilibration.

Vance and Fowler [5] studied serially changes in stores and in P_{CO_2} following a stepwise change in alveolar ventilation. Figure 7 shows their data on CO_2 stores changes versus time, with the appropriate curves from the computer added.

Mithoefer [7] has conducted experiments on rebreathing oxygen from bags containing various volumes of oxygen. The alveolar ventilation was increased about tenfold at the beginning of the experiment and maintained throughout the rebreathing period. Figure 8 shows the time changes in $P_{A_{CO_2}}$ in Mithoefer's experiments and those obtained from the computer data under simulated decrease in muscle perfusion.

It would appear therefore that the analogue is a fair reproduction of the physiological experiments and that the conclusions from the computer data can be applied to animal experiments, within the limiting frame of our assumptions.

A good example of the limiting value of our assumptions may be found in the excellent work of Lillehei and Balke [11] which disagrees with our calculated curves. The discrepancy is large (3.8 ml. kg. mm. P_{CO_2}) and not unexpected since in the experiment the final P_{CO_2} was about 15 mm. where the slope of the dissociation curve is higher than .45 vol. per cent/mm. The difference between actual and calculated results can be explained on this basis.

Effects of Direction of Change. When ventilation is decreased, additional CO_2 must be retained by the stores. This CO_2 must either be produced locally or brought in by blood. If perfusion is low, metabolism will be the only possible source of CO_2 and may become a limiting factor in the speed of stores readjustment. Obviously, the same problem does not arise during an increase in ventilation when there is loss of previously stored CO_2.

Conclusions

The analogue computer has allowed us to single out a certain number of parameters which must influence CO_2 stores equilibration. The crucial point appears to be the effect of muscle perfusion on the "functional" storage capacity of the body. It is this perfusion which changes potential storage capacity into an actual buffering system. If this perfusion differs between two experiments or changes during an experiment, an entirely new set of conditions will prevail and the results must be viewed accordingly.

Even under the most favorable conditions the body CO_2 stores must require several hours to adjust. With few exceptions all the data in the literature must be accepted as representing incomplete experiments in which time limitations did not allow full equilibration of the body stores.

There are large cyclic variations in alveolar CO_2 tension. In the light of our previous discussion we would postulate that since it takes the CO_2 stores several hours to readjust, there is a continuous change in stores, the steady state—if it ever occurs—being the exception rather than the rule.

The question which must be answered next is obvious: how long should re-equilibration be carried on? The dangers of relatively short experiments are clear. However, prolonged experiments suffer from drawbacks which are not less serious. Except in sacrifice experiments, where the whole animal [13] or parts [14, 15] are actually analyzed for CO_2 contents, the stores changes are calculated as the difference between actual CO_2 output and metabolic CO_2 output. The assumption of a basal CO_2 output over a period of several hours may be dangerous.

An entirely different objection for long equilibration is the fact that any change in CO_2 will alter the acid-base balance of the body and bring into play compensatory mechanisms. Nichols' data [15] show that after 5 hours of exposure to high CO_2 the muscle CO_2 has readjusted and remains practically unchanged. There is a questionable change in brain CO_2 but a significant, steady increase in blood CO_2. This must represent cation retention, as is usually found in respiratory acidosis. Extrapolation of the blood CO_2 content curve between 5 hours and 30 hours to time 0 reveals values measurably lower than at 5 hours, indicating that even during this time readjustment is already taking place.

Thus the investigation of the body CO_2 stores presents a real dilemma. Whether it is better to run the risk of terminating the experiment too soon, before complete equilibration, or chance the alternate danger of modifying the biological system will depend greatly on the investigator and the specific problem at hand.

Summary

The wide scatter in reported CO_2 storage capacity of the body must reside in a factor or factors which have not sufficiently been taken into account. In order to determine what these factors may be, data for the CO_2 storage capacity of various organs and their perfusion were collected. Using these data an electronic analogue was constructed. By simulating various procedures and varying the parameters, several experimental conditions were reproduced. Since most of the CO_2

storage capacity resides in the muscle, perfusion of the muscle mass will determine the rate at which this storage capacity may be brought into play. At rest, re-equilibration is always a lengthy process, requiring several hours. Under these conditions it should be concluded that most of the data in the literature were obtained fom experiments where not enough time had been allowed for equilibration.

Appendix

Construction of table 2 and of the analogue were limited by the lack of specific information concerning certain organs or tissues of the body. Several assumptions were required and some simplifications have been made. Under these conditions it becomes evident that the table represents more a method of thinking than a compilation of finalized data.

The first column in the table indicates the parameter studied and the unit in which this parameter is given. In the legend either the source or the method of obtaining the parameter is given. Basic information was taken from two sources [1, 11] and all other values were calculated from these according to the formula shown. When any data were used in the analogue the equivalents appear under the parameter. All the other rows represent compartments, *i.e.*, tissues or organs.

Exclusion of bone and fat from the table distorts considerably calculations of total body CO_2 content. However, it is probable that only a minimal error is introduced in the calculation of changes in CO_2 content (see text).

The simplification inherent to a classification of the whole body (except bone and fat) in five compartments is probably more damaging. Every compartment is assumed to be uniform, which is probably erroneous. In order to be able to isolate elements the basic data for each must be available. The error resulting from "idealizing" compartments by assuming uniformity cannot be predicted.

The first four parameters considered present no problem. Since the body is dealt with as separate compartments, the blood returning from each is considered separately. This "equilibrated blood volume" appears in line V. Its calculation is based on the assumption that each compartment contributes to the venous blood volume in proportion to its perfusion. The venous blood is assumed to be 75 per cent of the total volume, or 3,500 ml.

Using the Fick principle, the CO. output of every organ and its perfusion and the CO_2 content in the venous blood can be calculated, assuming an arterial content of 48 vol. per cent.

The partial pressure of CO_2 (line *VII*) is based on the assumption of an arterial P_{CO_2} of 40, a slope of the blood CO_2 dissociation curve of .45 vol. per cent/mm. P_{CO_2}, and on the venous CO_2 content calculated above. The partial pressure of CO_2 in the tissue is not known. Recent studies [18, 19] show that lymph has a P_{CO_2} higher than that of the venous blood draining the same area. If lymph gives a good indication of tissue tension, a large error in organ CO_2 content is probably introduced when one assumes tissue tension to be that of venous blood. However, if the difference in CO_2 tension between a compartment and the blood draining it remains constant (which is the assumption made), then *changes* in tissue CO_2 content can be calculated using venous P_{CO_2} values. The slope of the dissociation curve of the various tissues does not introduce any additional assumption. However, as better analytical methods become available, some of the figures will have to be revised.

If CO_2 is stored in the tissues as bicarbonate, this will necessitate hydration and the lack of carbonic anhydrase in a given tissue may prove a limiting factor in the storage capacity of an organ.

The slope of the dissociation curve of any tissue is assumed to be consant. This is not necessarily correct and may be affected by one of the following: (a) overall change in buffering capacity, as occurs during compensation of respiratory acidosis, (b) transfer of electrolytes from one compartment to another, (c) production of metabolites (such as lactic acid) which can displace CO_2 from bicarbonate, and (d) change in compartment volume.

Calculations for the alveolar compartment are slightly different. The equilibrated blood volume is assumed to be the total arterialized blood volume.

The kidneys have been excluded from the "other" compartment since their perfusion is extremely high (very low resistance) and their capacitance is necessarily small. Thus their time constant is practically nil. The capacitance of this system (which is mostly in the equilibrated blood volume) has therefore been added to that of the alveolar compartment.

Since the time constants of the heart, brain and "other" compartments are essentially similar, it is possible to replace these three compartments by an "equivalent compartment" without changes in the results or conclusions.

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