NONEQUILIBRIUM STEADY-STATE DIFFERENCES IN PARTIAL PRESSURE OF CO_2 AND IN CONCENTRATION OF WEAK ACIDS AND BASES BETWEEN BLOOD AND TISSUE

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ABSTRACT Several investigators have demonstrated that under conditions where little or no gas exchange occurs across the alveolar capillary membrane the P_{CO_2} is higher in the alveolus than in the mixed venous blood, whereas there are no P_{O_2} differences. Gurtner et al. have explained the ΔP_{CO_2} by a model in which H^+ dissociation of proteins due to an electrical field caused by a negatively charged capillary wall (Wien effect) sets up an intracapillary P_{CO_2} difference between wall and bulk phase which is maintained by blood flow. The model is not specific for CO_2 and predicts that weak acids should be concentrated in a manner similar to CO_2 whereas weak bases should be relatively excluded from the alveolar space. Measurements of the steady-state distribution of the uncharged forms of the weak acids 5,5-dimethyloxyazoladinedione (DMO) and barbital and of the weak base tris(hydroxymethyl)aminomethane (THAM) between mixed venous blood and a fluid-filled lobe of lung were made in living dogs. The results agree fairly well with the predicted values.

INTRODUCTION

Several investigators have found that under conditions of little or no gas exchange the partial pressure of CO_2 is higher in the alveolus than in the mixed venous blood or in the arterial blood (Denison et al., 1969; Gurtner et al., 1969; Guyatt et al., 1969; Jones et al., 1967; Jones et al., 1969). The difference between alveolar and mixed venous P_{CO_2} under conditions of no gas exchange will be referred to as ΔP_{CO_2}. Gurtner et al. found that the ΔP_{CO_2} was related both to H^+ and HCO_3^- activity (Gurtner et al., 1969).

A model was advanced by them to explain the experimental findings. The explanation postulated rapid movement of H^+ from blood buffers (proteins) toward a negatively charged capillary wall and a slower repulsion of $[HCO_3^-]$ away from the wall resulting in increased formation of H_2CO_3 and consequently molecular CO_2

near the wall. According to this hypothesis, the disequilibrium was maintained by blood flow.

Under conditions of no gas exchange the alveolar capillary membrane and alveolus would be in equilibrium with the higher CO_2 tension near the wall rather than the CO_2 tension of the bulk phase of capillary blood.

The rapid movement of H^+ ions is of crucial importance in this model and is thought largely to be due to the H^+ ion dissociation of large protein molecules when exposed to an electric field (Wien effect).[1]

Large negatively charged macromolecules such as proteins which move slowly by diffusion tend to lose their faster moving counterions (such as H^+, Na^+, etc.) when exposed to an electrical field. Since proteins are weak acids the loss of counterions, including H^+ ion near the charged groups on the protein molecule, causes dissociation of the acid groups. The proposed dissociation of protein causes the H^+ ion activity to reach equilibrium near the charged capillary wall faster than $[HCO_3^-]$ can escape because of electrostatic repulsion and thereby causes a transient production of CO_2 near the charged capillary wall due to the association of H^+ and HCO_3^-. If the transit time of blood through the capillary were shorter than the time for HCO_3^- to reach equilibrium, a steady-state P_{CO_2} difference could occur within the capillary, and consequently in the alveolar capillary membrane and alveolus. If the capillary transit time were sufficiently long, however, the effect of the increase of $[H^+]$ near the charged capillary wall would be balanced exactly by the effect of the decrease in $[HCO_3^-]$ and no differences in CO_2 would result.

We believe that under certain circumstances (high pulmonary blood flow rate) nonequilibrium of H^+, HCO_3^-, and CO_2 might occur within the capillary. Arguments supporting our belief in light of present knowledge concerning rates of chemical reaction and diffusion in blood are given in the Appendix of the paper of Gurtner et al.[2,3]

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[1] The Wien effect and the distribution of ions around fixed charges are discussed more fully in the paper of Gurtner et al. where further references can also be found.

[2] These are typographical errors in the Appendix of the paper of Gurtner et al. The equation, analogous to equation 2 here, on p. 184 should be:

$$X_2(t) = \Delta CO_2(t) = Ae^{-\lambda_2 t} - Ae^{-\lambda_1 t},$$

where A is defined as

$$\frac{X_1(0)(K_A)(\text{Heq})}{(\lambda_1 - \lambda_2)} \text{ and } X_1(0) = HCO_{3B} - HCO_{3eq}.$$

This can be shown to be the same as the above definition of A by substituting for λ_1 and λ_2 as defined above and rearranging.

[3] The second equation in the appendix of the paper of Gurtner et al. states that

$$\frac{dC_i}{dt} = \frac{a}{V} J_i EC + J \text{ chem } Rx,$$

where a represents the surface area across which the exchange is occurring and V represents the

QUANTITATIVE RELATIONSHIPS BETWEEN ΔP_{CO_2} AND BLOOD pH

If there is a difference in H^+ ion concentration between wall and bulk phase of capillary blood and if $[HCO_3^-]$ is assumed to be the same near the wall as in the bulk phase, the law of mass action leads to the following relationships:

$$H^+ = K_{[CO_2]} \frac{HC_2O_3}{HCO_3^-} = K_{[CO_2]} \frac{\alpha P_{CO_2}}{HCO_3^-},$$

$$\Delta H^+ = K_{[CO_2]} \frac{\alpha \Delta P_{CO_2}}{HCO_3^-}, \text{ and}$$

$$\frac{\Delta P_{CO_2}}{HCO_3} = \frac{\Delta H^+}{K_{[CO_2]}}, \tag{1 a}$$

where α is the solubility coefficient, and $K_{[CO_2]}$ is the effective equilibrium constant.

If the distribution of H^+ around a negative charge can be described by Boltzmann's distribution law then:[1]

$$H_w = H_B e^{+f\psi/RT},$$

where w indicates concentration near capillary wall, B indicates concentration in bulk phase, and ψ indicates potential difference between wall and bulk phase.

Since $\Delta H^+ = (H_w^+ - H_B^+)$, $\Delta H^+ = H_B^+ (e^{f\psi/RT} - 1)$, ΔH^+ at constant ψ is a constant multiple of H_B^+, and therefore, ΔP_{CO_2} should be directly related to H_B and inversely related to blood pH as follows:

$$\frac{\Delta P_{CO_2}}{HCO_3^-} = \frac{H_B^+(e^{f\psi/RT} - 1)}{\alpha K_{[CO_2]}}. \tag{1 b}$$

Gurtner et al. found that $\Delta P_{CO_2}/HCO_3^-$ increased in proportion to H^+ ion activity as predicted by equation 1 *b*.

The real situation is more complex, however, because $[HCO_3^-]$ near the wall is decreased by both the electrostatic repulsion of the negative charges and the chemical reaction forming CO_2. Gurtner et al. considered the rate of change of CO_2 and HCO_3^- activity in a small volume of blood passing through a pulmonary capillary under the influence of charges on the wall. In their treatment of the problem it is assumed that at time 0 the volume of blood enters the capillary and is acutely ex-

volume. Since we are interested in one-dimensional diffusion, V can be represented as a rectangular box which exchanges matter at one end represented by a, the area. Because of this a/V is equal to a/adx or $1/dx$. In their treatment of the problem Gurtner et al. omitted multiplying the J_iEC term by $1/dx$. For this reason they calculated that the thickness of a charged layer would have to be 100–500 A, which is larger than the Debye-Huckel theory would predict (4–20 times). When the multiplication is made, the required thickness is equal to 10–70 A, which agrees well with the Debye-Huckel theory.

posed to an electrical field. This assumption seems reasonable if it is kept in mind that the surface area of the pulmonary capillary bed is large compared with that of the pulmonary artery. Because of the difference in surface area it seems unlikely that blood entering the capillary near the wall would have been exposed to an electrical field near the wall of a pulmonary artery. This acute application of an electrical field causes the H^+ ion to reach equilibrium nearly instantaneously (because of the Wien effect). The H^+ ion then associates with HCO_3^- forming CO_2. It was shown that the relationship between ΔP_{CO_2} and time after exposure to an electrical field could be described by the following equation:[2]

$$\Delta P_{CO_2} = A(e^{-\lambda_2 t} - e^{-\lambda_1 t}), \tag{2}$$

where

$$\begin{aligned}
A &= (HCO_{3B}^- - HCO_{3eq}^-)/\alpha([K_{[CO_2]}/Heq] + 1),\\
HCO_{3B}^- &= \text{bulk } HCO_3^- \text{ concentration},\\
HCO_{3eq}^- &= (HCO_{3B})e^{-[f\psi/RT]} \text{ (the factor } e^{-f\psi/RT} \text{ comes from the Boltzmann distribution law)},\\
K_{[CO_2]} &= \text{effective equilibrium constant for } CO_2,\\
H^+eq &= [H^+ \text{ bulk}]e^{+f\psi/RT},\\
\lambda_1 &= (K_B + D/dx^2 + K_A[Heq]), \text{ and}\\
\lambda_2 &= D/dx^2.
\end{aligned}$$

D/dx^2 is the diffusion coefficient divided by the square of the thickness dx of the charged layer,[3] K_A and K_B are the effective forward and backward rate constants for the simplified reaction.

$$[H^+] + [HCO_3] \underset{K_B}{\overset{K_A}{\rightleftharpoons}} [CO_2] \text{ also } K_{[CO_2]} = \frac{K_B}{K_A}.$$

It can be seen that from equation 2 that the magnitude of ΔP_{CO_2} is a function of a number of factors, viz.

(*a*) H^+ and HCO_3^- concentration in the bulk phase.

(*b*) Electrical potential difference between wall and bulk phase.

(*c*) Diffusion coefficient and thickness of the charged layer (see footnote 3).

(*d*) Chemical reaction rate. It was shown that the reaction rate for dehydration of carbonic acid would have to be faster than the uncatalyzed rate for this mechanism to form significant amounts of CO_2; however, if the rates were 100 times faster than the uncatalyzed rate the ΔP_{CO_2} would be nearly as great as if the rate were infinitely fast. Roughton has estimated that the carbonic anhydrase activity inside red cells is sufficient to speed up the reaction 10,000-fold. Although several other enzymes appear to be present on the wall of pulmonary capillaries (Vane, 1969), carbonic anhydrase need not be present on the capillary wall since carbonic acid formed by

association of HCO_3^- and H^+ should be freely diffusible into the alveolar capillary membrane where the enzyme can facilitate the dehydration reaction. There is also evidence that the enzyme is present on the surface of red blood cells (Enns, 1971).

(*e*) The time that the blood is exposed to the electrical field. The time that the blood is in contact with the wall depends on the type of flow through the capillary. If there were strictly laminar flow this time may be long. Since the red cells are about the same size as the capillary, however, it seems likely that some mixing might occur due to the mechanical deformation of the cells. Mixing would tend to increase the quantity of blood exposed to the electrical field in a single transit time through the capillary and decrease in time that any volume of blood was under the influence of the charged capillary wall.

If there is mixing in the pulmonary capillary the time required for equilibration of blood with an inert gas present in the alveolus would obviously be shortened. Mixing, however, would, according to our hypothesis, tend to increase the magnitude of the P_{CO_2} gradient observed. The basis for this apparently paradoxical result is that mixing would cause a greater quantity of blood to be exposed to the electrical field in a single transit through the capillary bed and decrease the time that any volume of blood was under the influence of the charged capillary wall. The effect of mixing would thus be the same as decreasing the transit time through the capillary.

THE APPLICABILITY OF THE HYPOTHESIS TO OTHER WEAK ACIDS AND BASES

It should be noted that this mechanism should affect other weak acids and weak bases as well as CO_2.

Weak Acids

The differences predicted for weak acids can be calculated from equation 2.

Since nonvolatile weak acids do not undergo hydration and dehydration reactions, we can assume that the forward and backward rate constants are so fast that the factor $(e^{-\lambda_1 t})$ becomes negligible in comparison with the factor $(e^{-\lambda_2 t})$ as a function of time since λ_2 is a function of the rates of diffusion only where as λ_1 is dependent on reaction rate also.

If this assumption is made and we substitute ΔHA for $\alpha \Delta P_{CO_2}$, A^- for HCO_3^-, and $K_{[HA]}$ the equilibrium constant for the weak acid for $K_{[CO_2]}$ equation 2 becomes:

$$\frac{\Delta HA}{A^-} = \frac{(1 - e^{-f\psi/RT})}{K([HA]/H_B\, e^{+f\psi/RT}) + 1}\, e^{(-D/dx^2)t}. \qquad (3)$$

Since this hypothetical mechanism operates near the capillary wall in plasma; the pertinent diffusion coefficients for each weak acid should be related to the diffusion coefficient of the weak acid in water. Because these diffusion coefficients in water are similar we assume that the factor e^{-Dt/dx^2} is the same for the weak acids

to be studied. Furthermore, if the chemical reaction rates for CO_2 are fast enough (100 times the uncatalyzed rate) we can calculate the relationship between $\Delta CO_2/HCO_3^-$ and $\Delta HA/A^-$ for weak acids of different pK's on the basis of equation 3.

$$\frac{\Delta HA/A^-}{\Delta CO_2/HCO_3^-} = \frac{K_{[CO_2]} + H_B e^{+f\psi/RT}}{K_{[HA]} + H_B e^{+f\psi/RT}}. \quad (4)$$

In order to test these predictions we have measured the steady-state distribution of the nonmetabolized weak acids DMO, pK 6.12, and barbital, pK 7.8, between a fluid-filled lobe of lung in living dogs. In some cases simultaneous P_{CO_2} differences were also measured and compared with the simultaneous DMO and barbital differences.

Weak Bases

The predicted relationships for weak bases may be derived in a manner similar to that used for weak acids. If we consider the dissociation of the nonmetabolized weak base THAM (pK 7.77):

$$\frac{[H^+][T]}{[T^+]} = K_{[T]}.$$

The proton donor (T^+) analogous to CO_2 carries a positive charge; the proton acceptor (T) analogous to HCO_3^- is uncharged. According to the model the uncharged form of THAM should be lower near a charged capillary wall than in the bulk phase of capillary blood. By following reasoning similar to that used in the case of CO_2, H^+ ion would approach equilibrium very rapidly near the capillary wall (because of the Wien effect) while the movement of the charged proton donor (in this case toward the capillary wall) would be slower. During the time before equilibrium is reached some of the uncharged proton acceptor would associate with H^+ ion causing a transient decrease in the uncharged form. If the transit time of blood through the capillary is less than the time for equilibrium to occur, the uncharged form would be in lower concentration near the wall.

Since it is probably the uncharged THAM which diffuses across the alveolar capillary membrane, it would be in lower concentration in the membrane than in the bulk phase of the capillary blood. If, in the experimental preparation, the alveoli were filled with liquid, the concentration of uncharged THAM in the alveoli would be expected to be lower than in the bulk phase of the blood.

The quantitative relationship can be worked out in a manner similar to those for weak acids and is as follows:

$$\frac{-\Delta T}{T^+} = \frac{(e^{+f\psi/RT} - 1)}{1 + [(H_B e^{+f\psi/RT}/(K_{[T]})} e^{-(D/dx^2)t}. \quad (5)$$

The negative sign on the left indicates that uncharged THAM should be lower in the alveolar fluid than in the blood. Furthermore, the absolute value of $-\Delta T/T^+$ should increase as H_B is decreased.

The predicted ratio between $-\Delta T/T^+$ and $\Delta CO_2/HCO_3^-$ can be calculated by dividing equation 3 by equation 5 assuming e^{-Dt/dx^2} is the same for both. It is:

$$\frac{-\Delta T/T^+}{\Delta CO_2/HCO_3^-} = \frac{e^{+f\psi/RT}\,(K_{[CO_2]}\,K_{[T]} + K_{[T]}\,H_B\,e^{+f\psi/RT})}{(H_B^2\,e^{+2f\psi/RT} + K_{[T]}H_B\,e^{+f\psi/RT})} \quad . \qquad (6)$$

To test this prediction we measured steady-state distribution of THAM between a fluid-filled lobe of lung in living dogs and compared the distribution of THAM with the simultaneously measured CO_2 differences.

MATERIAL AND METHODS

Experiments were performed on dogs weighing between 10 and 20 kg, anesthetized with pentobarbital. A catheter with a tiny inflatable cuff was placed in the right lower or mediastinal lobe bronchus and the cuff was inflated. After degassing the lobe by replacing the air in the lobe with oxygen and allowing the lobe to collapse, 60–90 cc of an isosmotic solution was instilled. Either sucrose, dextran, or plasma was used. After ¼ hr, control samples of alveolar fluid and mixed venous blood were taken and used to count background radiation. After the control samples were taken 5–15 μCi of ^{14}C-labeled DMO, barbital, or THAM was infused into the pulmonary artery. Paired samples of alveolar fluid and mixed venous blood were taken over the next several hours and analyzed for P_{CO_2}, pH, and counted in a Packard Tri-Carb liquid scintillation counter (Packard Instrument Co., Inc., Downers Grove, Ill.).

All the samples were prepared for radioactive counting in the same way. The proteins in serum and alveolar fluid were precipitated using trichloroacetic acid, and the samples were added to a Triton, toluene, 2,5-diphenyloxazole (PPO), and *p*-bis[2-(5-phenyloxazolyl)] benzene (POPOP) liquid scintillation cocktail.

The counts in all cases are expressed as counts per volume of water which the sample contained. The water content of alveolar samples and plasma was determined by weighing before and after drying in a heated vacuum evaporator. Most experiments were done on animals paralyzed with succinylcholine and mechanically ventilated. The animal's pH was increased by increasing minute ventilation and decreased by adding CO_2 to the inspired air. Since all of the compounds used traverse the alveolar capillary membrane slowly, blood pH was kept constant after infusion of the isotope into the systemic circulation.

The uncharged proportion of the weak acids and bases were calculated from the measured pH values and counts using the pK values mentioned above.

RESULTS

$\Delta DMO/DMO^-$ is plotted in Fig. 1 *a* against the $[H^+]$ concentration of mixed venous blood. The solid line on Fig. 1 *a* is calculated from equation 3 assuming that ψ = 7.5 mv and t = 0. This line is included only to show the shape of the predicted relationship. Similar predicted relationships are included in Fig. 2 *a* and 3 *a* for barbital and THAM using the assumption that t = 0 (see Discussion).

Since the pK of DMO and CO_2 are almost identical, equation 4 in this case pre-

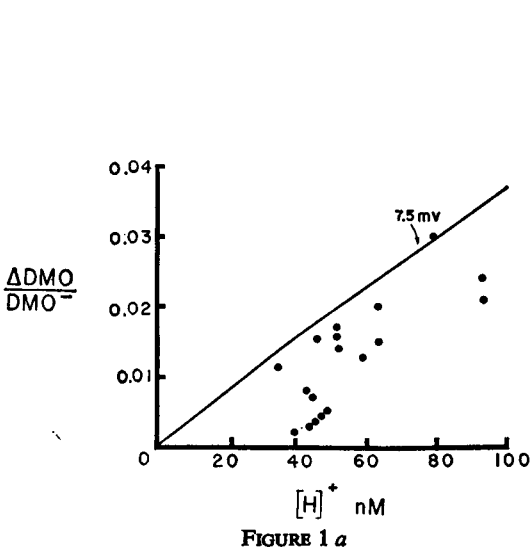

FIGURE 1 *a*

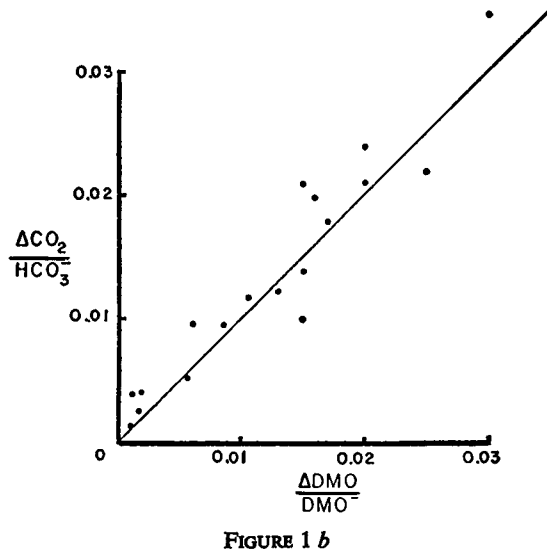

FIGURE 1 *b*

FIGURE 1 *a* The difference in uncharged DMO concentration between alveolar fluid and mixed venous blood (ΔDMO) divided by the venous concentration of the charged form (DMO^-) is plotted against the H^+ activity of mixed venous blood. The solid line gives the predicted relationship assuming a 7.5 mv potential difference between wall and bulk phase of the capillary blood (see text).

FIGURE 1 *b* The relationship between simultaneously measured $\Delta DMO/DMO^-$ and $\Delta CO_2/HCO_3^-$. The solid line gives the predicted relationship according to equation 4 (unity in this case since $K_{[DMO]} = K_{[CO_2]}$).

dicts that $\Delta DMO/DMO^- : \Delta CO_2/HCO_3^-$ measured in the same samples should be one. In Fig. 1 *b* $\Delta DMO/DMO^-$ is plotted against simultaneously measured $\Delta CO_2/HCO_3^-$. The values do not differ from the predicted relationship.

Barbital

$\Delta B/B^-$ is plotted against $[H^+]$ concentration of mixed venous blood in Fig. 2 *a*. The theoretical relationship for a potential difference of 7.5 mv is given as the solid line (see Discussion). The ratio of $\Delta B/B^-$ and $\Delta CO_2/HCO_3^-$ is given in Fig. 2 *b* as a function of mixed venous $[H^+]$ concentration. The solid lines give the predicted values of $\Delta B/B^- : \Delta CO_2/HCO_3^-$ as given by equation 4 for potential differences of 7.5 and 17.5 mv. The closed circles represent simultaneously measured $\Delta CO_2/HCO_3^-$ and $\Delta B/B^-$. The closed squares represent mean $\Delta CO_2/HCO_3^-$ and $\Delta B/B^-$ from Fig. 2 *a* and from the paper of Gurtner et al.; from H^+ of 30–80, one standard error of the mean range is given.

THAM

$-\Delta T/T^+$ is plotted against $[H^+]$ concentration of mixed venous blood in Fig. 3 *a*. The solid lines indicate the predicted values for 7.5 and 17.5 mv from equation 5.

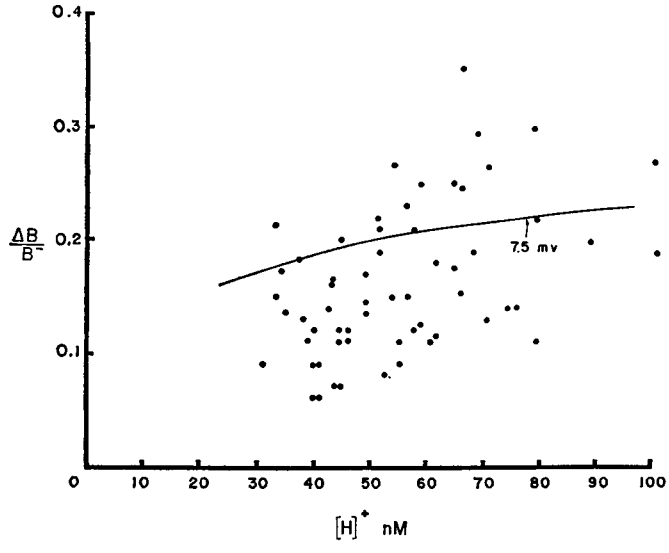

FIGURE 2 *a* The relationship between $\Delta B/B^-$ and H^+ activity. The predicted relationship for a potential difference of 7.5 mv between wall and bulk phase is given by a solid line (see text).

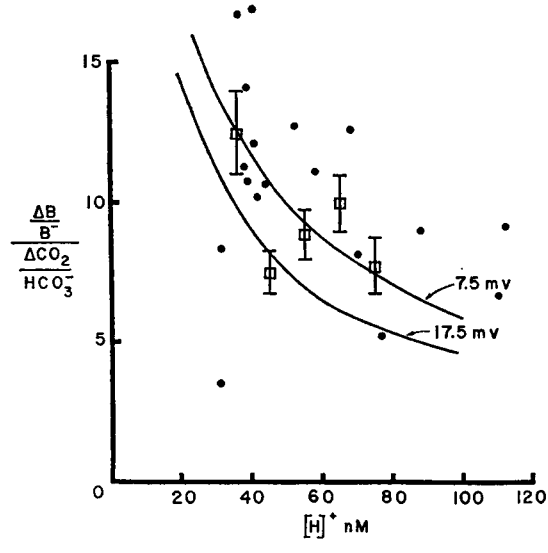

FIGURE 2 *b* The relationship between simultaneously measured $\Delta B/B^-$ and $\Delta CO_2/HCO_3^-$ and the average relationship ± one standard error of the mean, from nonsimultaneous measurements from Fig. 2 *a* and from the paper of Gurtner et al. 1969. The solid lines give the relationship for 7.5 and 15 mv predicted by equation 4.

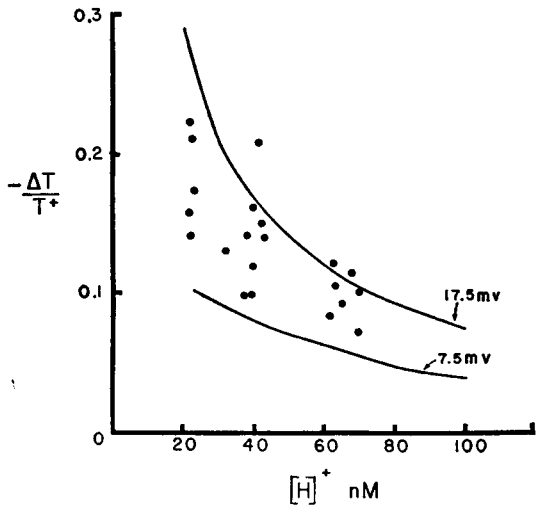

FIGURE 3 *a*

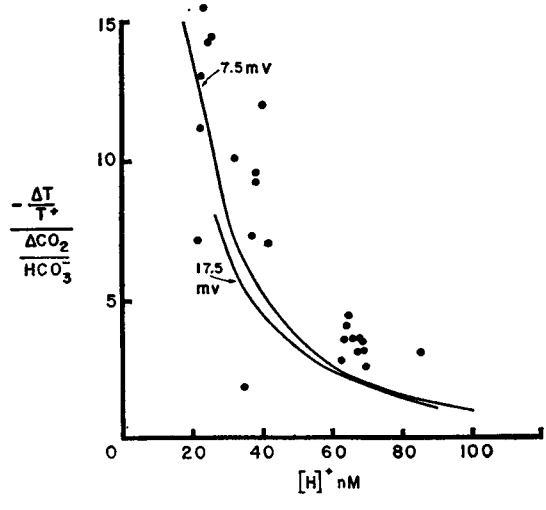

FIGURE 3 *b*

FIGURE 3 *a* The relationship between $-\Delta T/T^+$ and H^+ activity of mixed venous blood. The relationship predicted for a potential difference of 7.5 and 15 mv between wall and bulk phase is given by the solid lines (see text).

FIGURE 3 *b* The relationship between simultaneously measured $-\Delta T/T^+$ and $\Delta CO_2/HCO_3^-$ is plotted against the H^+ ion activity of the mixed venous blood. The solid lines give the relationship predicted by equation 6 for a potential difference of 7.5 and 15 mv.

The ratio of $-\Delta T/T^+$ and $\Delta CO_2/HCO_3^-$ measured simultaneously is given in Fig. 3 *b*. The solid lines give the predicted ratios from equation 6.

DISCUSSION

It seems that $\Delta DMO/DMO^-$, and $-\Delta T/T^+$ do not differ markedly from the theoretical relationships predicted by the model in that $\Delta DMO/DMO^-$, $\Delta B/B^-$, and $-\Delta T/T^+$ are close to the theoretical relationship for a potential difference of 7.5 mv. It should be pointed out that the theoretical lines in Figs. 1 *a*, 2 *a*, and 3 *a* are drawn merely to show the shape of the predicted relationship between the difference ratios and not to mean that the potential difference between wall and bulk phase is 7.5 mv. It can be seen from equations 4 and 6 that these predicted relationships would only apply if transit time (t) through the capillary were 0 (i.e., infinitely fast blood flow). Thus 7.5 mv appears to be the lower limit of potential necessary to produce the observed differences. It is not possible to calculate an upper limit of potential from equations 3 and 5 as a number of combinations of ψ, D/dx^2, and t may give the same weak acid and base differences. It seems, however, from Figs. 2 *b* and 3 *b* that values of from 7.5 to 17.5 mv fit the data fairly well. Such potential differences due to fixed charges are frequently encountered in biology; for example the charged groups on the surface of a red blood cell give rise to a negative potential difference of about 17–18 mv between surface and bulk phase.

CONCERNING THE UNIQUENESS OF THE CHARGED MEMBRANE HYPOTHESIS

Although the proposed mechanism explains the experimental data, it may not be the only explanation. Therefore, it seems of interest to examine other possible hypotheses to ascertain closeness of it for other mechanisms. A number of possible alternatives were considered by Gurtner et al.; these will not be reviewed here. Some additional possibilities, however, have arisen.

A possible alternative theory is that proposed by Stephens et al. (1969) to explain fluxes of weak acids and bases against a concentration gradient across the epithelium of the rumen of sheep. In this hypothesis the source of H^+ ion is a metabolically maintained H^+ difference between cells and extracellular fluid. If there is movement of the charged form of weak acid across the cell membrane, a difference in uncharged form will result depending on the ratio of the permeability of charged to uncharged forms.

The relationship between intracellular and extracellular H^+ at different extracellular pH's is not known for the cells making up the alveolar capillary membrane. In skeletal muscle the difference between intra- and extracellular H^+ ion activity decreases as pH decreases if pH changes were caused by changing CO_2 tension as in these experiments (Adler et al. 1965). This means that $\Delta HA/A^-$ should decrease rather than increase if caused by this mechanism.

The equations describing the above model were derived by Roos (1965) and Stephens et al. (1969). Using these equations one can calculate the magnitude of $\Delta HA/A^-$ for different extracellular pH's and permeability ratios for the dissociated and undissociated forms for this mechanism. Even if one assumes that there is a constant ΔpH across the cell membrane (0.4 pH units), it is necessary for a weak acid with a pK of 6.12 to have a permeability ratio of dissociated to undissociated form of 1/40 for an HA/A of 0.01 to occur at an extracellular pH of 7.4. This means that the ratios of permeability of DMO and CO_2 would have to be identical in order to have similar differences. If HCO_3^- permeability in the alveolar capillary membrane is similar to other anions, the ratio of CO_2 to HCO_3^- permeability should be orders of magnitude greater than the ratio of DMO to DMO^- permeability.

If the extracellular pH is decreased at a constant transmembrane pH the increase in $\Delta HA/A$ predicted by this model is less than that actually observed. We observed that with CO_2 and DMO change in pH from 7.4 to 7.0 causes $\Delta HA/A^-$ to increase approximately from 0.01 to 0.03 whereas the increase in $\Delta HA/A^-$ predicted by Roos's equations is from 0.01 to 0.0105.

The model predicts a decrease in $\Delta HA/A^-$ for a weak acid of pH 7.8 with permeability ratio of 1/4 under the above conditions. The 1/4 permeability ratio is required for the theoretical $\Delta HA/A^-$ for barbital to match the observed value at a blood pH of 7.4.

Thus, even if rather unrealistic assumptions are made as to mobility of CO_2 and

HCO_3^- and the differences in pH across cell membranes during respiratory acidosis, the model does not fit our data.

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REFERENCES

ADLER, S., A. ROY, and A. RELMAN. 1965. *J. Clin. Invest.* **44**:8.
DENISON, D., R. H. T. EDWARDS, G. JONES, and H. POPE. 1969. *Resp. Physiol.* **7**:326.
ENNS, I. 1971. *Fed. Proc.* **30**(2):493. (Abstr.)
GURTNER, G. H., S. H. SONG, and L. E. FARHI. 1969. *Resp. Physiol.* **7**:173.
GUYATT, A. R., C. J. YU, B. LUTHERER, and A. B. OTIS. 1969. *Fed. Proc.* **28**(2):719. (Abstr.)
JONES, N. L., E. J. M. CAMPBELL, G. J. R. MCHARDY, B. E. HIGGS, and M. CLODE. 1967. *Clin. Sci. (London).* **32**:311.
JONES, N. L., E. J. M. CAMPBELL, R. H. T. EDWARDS, and W. G. WILKOFF. 1969. *J. Appl. Physiol.* **27**:356.
ROOS, A. 1965. *Amer. J. Physiol.* **209**:1233.
ROUGHTON, F. J. W. 1969. Handbook of Physiology. Sect. 3: Respiration. American Physiological Society, Washington D.C. **1**:810–813.
STEPHENS, G. E., A. DOBSON, and J. H. MAMMANO. 1969. *Amer. J. Physiol.* **216**:983.
VANE, J. R. 1969. *Brit. J. Pharmacol. Chemother.* **35**:209.