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Research Article

CONSIDERATIONS ON THE UPTAKE OF CARBON MONOXIDE BY THE LUNGS[1]

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In the course of investigations upon the disappearance of CO from the alveolar gas during breathholding following a single inspiration of a gas containing CO (1) we found it necessary to consider the effect of variations of this process in the different alveoli upon the behavior of the lung as a whole. The following discussion contains the more useful of these considerations, first for circumstances during breathholding (A) and secondly for circumstances during the steady state breathing of a gas mixture containing CO (B). Section C discusses the effect of significant amounts of COHb in the mixed venous blood upon the rate of CO uptake from the lungs, knowledge which was necessary in interpreting our results in experiments on heavy smokers. Section D considers the build-up of alveolar CO concentration, as the subject starts breathing a mixture containing CO. In other words, it describes the washout of the alveolar gases and achievement of the so called "steady state" condition before the mixed venous blood COHb concentration rises significantly. The final section E is a brief discussion of the build-up of COHb in the blood when the subject breathes CO for such long periods of time, that the processes covered in the earlier sections can be considered instantaneous.

A. *The Relation between the Mixed Expired Alveolar CO Tension and Time after a Single Inspiration of a Gas Containing CO*

In 1909, Krogh and Krogh (2) described the disappearance of CO from alveolar gas during a period of breathholding following a single inspiration of gas containing CO by the equation

$$F_A = F_{A_0} \exp\left(-\frac{DPbt}{V_A}\right), \qquad (1)$$

where F_A is alveolar concentration of CO (dry) at time t, F_{A_0} is alveolar concentration (dry) at time zero, "exp" is e, the base of the natural logarithms raised to the power contained in the brackets following, D is the pulmonary diffusing capacity for CO in ml. STPD/mm. Hg × sec, V_A is the total alveolar gas volume during the period of breathholding in ml. STPD, and Pb is the barometric pressure in mm. Hg minus 47 mm. Hg.

In order to derive Equation *1*, Krogh had to assume that (a) the CO concentration was equal in all alveoli of the lungs and (b) that the plasma CO tension was negligible. The calculations of Rauwerda (3) suggest that it is permissible to assume that little or no CO gradient would exist within the gas of a single alveolus. However, recent studies on uneven ventilation (4) make it highly probable that the initial alveolar CO concentration varies among different alveoli after a single inspiration of a gas containing CO. Assumption (b) has been questioned by Roughton (5) because the rate of combination of CO with hemoglobin in human red cells at 37° C. is sufficiently slow in relation to the rate of CO diffusion from alveolar gas into the capillary blood that a significant tension of CO must be present in the blood. At this juncture it should be pointed out that capillary CO tension may be significant either because the mean capillary COHb concentration is large or because the diffusing capacity in the alveolus is large in relation to the rate of combination of CO and Hb. This latter CO tension will disappear in the arterial blood, because the reaction of CO and Hb will continue after the blood has left the alveolus.

Therefore, the two assumptions (a) and (b) are invalid to some degree. In a separate paper

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(6) the uptake of CO from a single alveolus during breathholding and during steady state breathing of a gas mixture containing CO is investigated. Obviously the entire discussion cannot be reproduced here. For the purpose of this paper the decrease in alveolar CO concentration with time during breathholding can be expressed as

$$F_A = F_{A_0} \exp\left(-\frac{DPbCt}{V_A}\right), \qquad (2)$$

where C is a correction factor[4] to allow for the fact that the plasma CO tension is not negligible.

Since it can no longer be assumed that the alveolar CO concentration is equal throughout the lung, the changes of CO concentration in the gas that we can sample, namely the mixed[5] expired alveolar gas, must be studied. The mixed expired alveolar CO concentration can be described as the sum of the concentrations of the different alveoli, weighted according to their fractional contribution to the expired sample. Thus:

$$\overline{F_{AE}} = \sum_{1}^{N} \phi_i F_{AEi}, \qquad (3)$$

where $\overline{F_{AE}}$ is the mixed expired alveolar CO concentration, ϕ_i is the fraction contributed by the ith alveolus, F_{AEi}[6] equals the CO concentration in the ith alveolus, and N is the number of alveoli. When the alveolar CO concentration as given by Equation *2* is substituted in Equation *3*, we obtain

$$\overline{F_{AE}} = \sum_{1}^{N} \phi_i F_{AOi} \exp\left(-\frac{D_i PbC_i t}{V_{Ai}}\right). \qquad (4)$$

F_{AOi}, the initial CO concentration in the ith alveolus equals $\frac{(V_T - V_D)_i}{V_{Ai}} F_I$, where $(V_T - V_D)_i$ equals the inspired volume reaching the alveolus, V_{Ai} equals the alveolar volume during the period of breathholding, and F_I equals the inspired CO concentration (dry). Substituting this expression for F_{AOi} in Equation *4*, we obtain

$$\overline{F_{AE}} = F_I \sum_{1}^{N} \phi_i \frac{(V_T - V_D)_i}{V_{Ai}} \exp\left(-\frac{D_i PbC_i t}{V_{Ai}}\right). \qquad (5)$$

$\overline{F_{AE}}$ consists of the sum of a series of exponential decay terms, each exponent of which may be different, and equals $-\frac{D_i PbC_i}{V_{Ai}}$. The zero intercept or the value of $\overline{F_{AE}}$ when t = 0, is $F_I \sum_{1}^{N} \phi_i \frac{(V_T - V_D)_i}{V_{Ai}}$. This intercept represents the sum of the initial concentration in each alveolus multiplied by the fraction of the expired sample contributed by that alveolus. Since there are a great number of alveoli in the lung one would expect to find many with the same decay constant. Such similar alveoli can be considered together and will be termed a ***diffusing phase.*** The different alveoli constituting a "phase" are not necessarily located near each other.

It is interesting to consider the log $\overline{F_{AE}}$, because this form is useful in solving for D, the pulmonary diffusing capacity.

$$\log \overline{F_{AE}} = \log F_I + \log \sum_{1}^{N} \phi_i \frac{(V_T - V_D)_i}{V_{Ai}} \times \exp\left(-\frac{D_i PbC_i t}{V_{Ai}}\right). \qquad (6)$$

This need not be a straight line, as is suggested by consideration of Equations *1* or *2* alone. However, if all exponents are equal, then Equation *6* becomes

$$\log \overline{F_{AE}} = \log F_I \sum_{1}^{N} \phi_i \frac{(V_T - V_D)_i}{V_{Ai}} - \frac{D_i PbC_i t}{V_{Ai}} \log_{10} e. \qquad (7)$$

[4] $C = \frac{1}{1 + \frac{D}{\theta V_c}}$.

θ is the average rate of combination of CO with the hemoglobin in the corpuscle under specific conditions of oxygenation, temperature and pH encountered along the pulmonary capillary, expressed in ml. CO STPD combining/sec. × ml. of blood × mm. CO tension plasma. V_c is the volume of blood in the pulmonary capillaries in ml.

[5] "Mixed" is indicated by a bar over the symbol ($\overline{F_{AE}}$ which equals *mixed* expired alveolar CO concentration), and signifies that the sample contains gas from more than one alveolus. "Mean" is indicated by a heavy bar over the symbol ($\overline{F_{AE}}$ which equals *mean* expired alveolar CO concentration) and signifies that the sample contains gas collected during an entire respiratory cycle.

[6] The CO concentration is considered equal throughout an alveolus and the time of expiration is considered negligible so that the expired alveolar concentration equals the alveolar concentration.

This is a straight line relationship. Thus one of the conditions for log $\overline{F_{AE}}$ versus time to be a straight line as Krogh assumed is that the decay constants of all parts of the lung must be equal. It is important to note that if the exponents are all equal log $\overline{F_{AE}}$ will be linear regardless of the unevenness of ventilation. The exponents will be equal if $\frac{D_i C_i}{V_{A_i}}$ is equal in the different alveoli. C_i $\left(\text{which equals } \frac{1}{1 + \frac{D_i}{\theta_i V_{c_i}}}\right)$ depends on the diffusing capacity of the alveolus (D_i) the volume of capillary blood in the alveolus (V_{ci}) and on the rate of combination of CO with Hb (θ_i). Although θ varies with alveolar O_2 tension, increasing slightly with a decreasing O_2 tension, the factor C_i would be expected to vary less throughout the lung than D_i/V_{A_i}, the diffusing capacity per unit alveolar gas volume. The extent of variation of these quantities in the lung is unknown at present, although the disappearance of CO from the alveoli is not exponential (1). The problem of obtaining the true total pulmonary diffusing capacity in the face of variations in D_i/V_{A_i} throughout the lung is a matter for future study.

B. *The Uptake of CO under "Steady State" Conditions*

Under special conditions and for short periods of time, a subject who has started to breathe CO reaches a so-called "steady" state. In this condition, $\overline{F_A}$, the mean alveolar CO concentration in a single phase is constant from breath to breath. In other words, the amount of CO removed from the inspired gas during a respiratory cycle equals that being taken up by the blood. Stated mathematically when venous COHb equals 0,

$$f(V_T - V_D)(F_I - \overline{F_{AE}}) = D\overline{F_A}PbC, \quad (8)$$

where F_I is the inspired concentration of CO (dry), f is the frequency of respiration per second, $\overline{F_{AE}}$ is the mean in time of the expired alveolar CO concentration, and $\overline{F_A}$ is the mean in time of the alveolar concentration. $\overline{F_{AE}}$ does not necessarily equal $\overline{F_A}$, because $\overline{F_A}$ is a mean over the whole respiratory cycle, while $\overline{F_{AE}}$ is expelled only during the expiratory phase of the respiratory cycle. However, it is more convenient to let $\overline{F_A} = \overline{F_{AE}}$ in Equation *8* and change D to D′. This indicates that the value of D′ obtained from the application of the "steady state" principle is not necessarily equal to the true D. If $\overline{F_{AE}}$ is substituted for $\overline{F_A}$ in Equation *8* and the latter is then solved for $\overline{F_{AE}}$, we obtain

$$\overline{F_{AE}} = \frac{F_I}{1 + \frac{D'PbC}{f(V_T - V_D)}}. \quad (9)$$

However, just as in the case of the fall in CO during breathholding, we cannot obtain gas from the individual alveoli, but must be content with an average sample from the whole lung. For the "steady state" circumstances this expired sample is a mean mixed expired sample ($\overline{\overline{F_{AE}}}$): it is a mean in time over most of the respiratory cycle and a mixture of contributions from different alveoli.

$$\overline{\overline{F_{AE}}} = \sum_{1}^{N} \frac{(V_T - V_D)_i}{V_T - V_D} \overline{F_{AE_i}}. \quad (10)$$

Substituting the value of F_{AE} for an individual alveolus given by Equation *9* in Equation *10*, we obtain

$$\overline{\overline{F_{AE}}} = \frac{F_I}{V_T - V_D} \sum_{1}^{N} \frac{(V_T - V_D)_i}{1 + \frac{D_i'PbC_i}{f(V_T - V_D)_i}}. \quad (11)$$

The total pulmonary diffusing capacity $\left(\sum_{1}^{N} D_i' = D'\right)$ has been computed by dividing the CO uptake per minute by the mean mixed expired alveolar CO tension (2, 5). It is important to note that this is not correct unless the lung is considered a single diffusing/ventilating phase. Thus if total pulmonary diffusing capacity is calculated by dividing the total CO uptake per minute by the mean mixed expired alveolar CO tension,[7]

$$aD' = \frac{f(V_T - V_D)(F_I - \overline{\overline{F_{AE}}})}{Pb\overline{\overline{F_{AE}}}}. \quad (12)$$

[7] This, of course, assumes the plasma CO tension is negligible, *i.e.*, C = unity. Obviously this is not true, but (a) it has been done (b) it has a certain clinical usefulness and (c) it does not alter the force of the discussion. Any alternate presentation appears unnecessarily complicated.

aD′ is the apparent pulmonary diffusing capacity of the whole lung. This letter "a" for "apparent" will be used to indicate that the value of D′ was obtained from mixed alveolar air from the entire lung without regard for variations in the diffusing-ventilating ratios of the different alveoli. When the value of $\overline{\overline{F_{AE}}}$ from Equation *11* is substituted herein

$$aD' = \frac{f(V_T - V_D)}{Pb}\left[\frac{(V_T - V_D)}{\sum_1^N \frac{(V_T - V_D)_i}{1 + \frac{D_i'PbC_i}{f(V_T - V_D)_i}}} - 1\right]. \qquad (13)$$

aD′ will equal the true total D′ if $\frac{D_iPbC_i}{f(V_T - V_D)_i}$ is the same throughout the lung. As discussed above, this condition is dependent mainly on $D_i'/(V_T - V_D)_i$ remaining the same throughout since C_i has been considered unity. The condition of constant $D_i'/(V_T - V_D)_i$ is actually a condition of maximum efficiency, where the ventilatory gas is distributed proportionally to the available diffusing surface. Any deviation from this ideal condition will make aD′ less than the actual D′. It must be noted that this condition is not the same as the major requirement that mean expired CO fall exponentially with time, which is that $\frac{D_i}{V_{A_i}}$ be constant throughout the lung.

The fractional CO uptake

$$\left(\frac{\text{CO inspired in ml./min.}}{\text{CO absorbed in ml./min.}}\right)$$

has been investigated by a number of workers (7–9). The CO uptake per minute of any alveolus equals $f(V_T - V_D)_i(F_I - \overline{F_{AE}})_i$ (see Equation *8*). Therefore the CO uptake per minute for the whole lung is $f\sum_1^N (V_T - V_D)_i(F_I - \overline{F_{AE_i}})$. Using the value of $\overline{F_{AE_i}}$ given by Equation *9*, since the inspired CO is fV_TF_I, fractional CO uptake in per cent

$$= \frac{100}{fV_T}\sum_1^N \frac{1}{\frac{1}{f(V_T - V_D)_i} + \frac{1}{D_i'PbC_i}}. \qquad (14)$$

It is clear from this equation that changes in fractional CO uptake cannot be related to changes in pulmonary diffusing capacity unless the relationship of D′, $V_T - V_D$ and C are known for all parts of the lung. Disregarding for the moment any question of variations in $D_i'C_i/(V_T - V_D)_i$ throughout the lung, an increase in D′ will cause an increased fractional CO uptake which seems reasonable. Note however that an increase in minute ventilation (fV_T) will cause a decrease in fractional CO uptake (9) (except at extremely low tidal volumes). If we include the possibility of variation in $D_i'C_i/(V_T - V_D)_i$ in the lung, a change in ventilation pattern could cause a decrease in fractional CO uptake even though total diffusing capacity and total ventilation were kept constant. It can be shown that the fractional CO uptake will be maximal when the two terms of the denominator of Equation *14* are in the same ratio in all phases. The fractional CO uptake in the presence of uneven distribution of gas within the lung will be influenced more by the diffusing capacity of overventilated parts of the lung than of the underventilated parts.

It must be emphasized that the assumption that respiration is a continuous process is certainly not true and use of Equation *14* to correct for the effect of changes in effective ventilation $f(V_T - V_D)$ upon the fractional CO uptake may fail in extreme cases for this reason.

C. *The Effect of the Presence of COHb in the Mixed Venous Blood*

In all discussions up until this point, it has been assumed that the mixed venous blood had no significant amount of COHb in it. Under normal circumstances this is true, but after periods of breathholding approaching a minute, the alveolar CO concentration falls to levels where the tension of CO in equilibrium with the venous blood becomes important in smokers. Therefore, it is often necessary to make a correction for the mixed venous COHb. This problem is discussed in more detail in another paper (6) but for present purposes it will suffice to say that since all the processes discussed above are exponential, we should deal with the difference between the alveolar CO concentration and its value at equilibrium, rather than the alveolar CO concentration alone.

In the cases already discussed the equilibrium value has been zero, but in cases where the mixed venous COHb is significant, the equilibrium value becomes greater than zero. When the alveolar O_2 tension is high enough to ensure saturation of the Hb, as when 100 per cent O_2 is inspired, the equilibrium CO concentration can be calculated from the Haldane relationship (10),

$$F_c = \frac{F_{cO_2}COHb}{MO_2Hb}. \quad (15)$$

F_c is the CO concentration, F_{cO_2} the O_2 concentration of gas in equilibrium with the blood. COHb and O_2Hb are the concentrations of the respective compounds expressed in volumes of gas (STPD) combined per volume of blood. Aside from questions as to the exact value of M, which is approximately 210, this equation is almost precisely correct when 100 per cent O_2 is inspired, because the capillary O_2 tension becomes equal to the alveolar O_2 tension near the venous end of the capillary, and the CO tension in the plasma will build up from what it was in the mixed venous blood to correspond to the value given by Equation *15* equally rapidly. With lower alveolar O_2 tensions the use of the Haldane relation becomes less exact, but because the COHb concentration is almost always less than 0.02 ml. gas per ml. blood (2 vols. per cent) in the mixed venous blood, the error involved is usually negligible.

Substituting (alveolar CO concentration-equilibrium alveolar CO concentration) for alveolar CO concentration, the expired alveolar CO concentration of a single alveolus during breathholding following a single inspiration of a gas containing CO becomes

$$F_{AE} = \left[F_I \frac{V_T - V_D}{V_A} - \frac{F_{cO_2}COHb}{MO_2Hb}\right] \times \exp\left(-\frac{DPbCt}{V_A}\right) + \frac{F_{cO_2}COHb}{MO_2Hb}. \quad (16)$$

Similarly, the mixed expired alveolar CO concentration during breathholding (Equation *5*) becomes

$$\overline{F_{AE}} = \sum_1^N \phi_i \left[\frac{(V_T - V_D)_i F_I}{V_{Ai}} - \frac{COHbF_{cO_2i}}{MO_2Hb}\right] \times \exp\left[-\frac{D_i PbC_i t}{V_{Ai}}\right] + \sum_1^N \phi_i \frac{COHbF_{cO_2i}}{MO_2Hb_i}. \quad (17)$$

The last term containing COHb is a summation, weighted according to the contribution of each phase. In practice the entire term is small, and can be calculated from average values of COHb, O_2Hb and F_{cO_2}.

Analogous equations can be obtained for the steady state conditions, but are more involved than the equations above and will not be reproduced here. It is more convenient to change the variable in the equations already given in the previous section on the steady state conditions. This simply means subtracting the equilibrium value of CO concentration $(COHbF_{cO_2})/MO_2Hb$ from F_A and F_I, and substituting these new values in the given equations.

D. *The Relation between Expired Alveolar CO Concentration and Time Considering Respiration a Continuous Process and the Lung as a Single Bag*

The circumstances considered in this section deal with a subject who starts to breath a mixture containing CO. The equations are concerned with the washout of the original gases in the alveoli, and the attainment of a steady state where the CO brought to the alveoli by the ventilation equals that carried away by the blood. This washout process is essentially complete before the mixed venous blood COHb becomes significant. Respiration is considered to be a continuous process. Variations in ventilation, or diffusion throughout the lung are ignored, because of complexity, and the lung is considered a perfectly mixed bag.

The rate of change of CO contained in the lung gases $\frac{(d\overline{F_A}V_A)}{dt}$ equals the net rate at which CO is carried to the lung by ventilation $(V_T - V_D)f(F_I - \overline{F_{EA}})$ less the rate at which it is carried away by diffusion into the blood $(\overline{F_A}aD'PbC)$. Thus

$$\frac{d\overline{F_A}V_A}{dt} = f(V_T - V_D)(F_I - \overline{F_{AE}}) - \overline{F_A}aD'PbC. \quad (18)$$

The difference between the inspired and expired gas volumes has been ignored. Note that the factor C has been included to allow for the fact that plasma CO tension is not always negligible. Since respiration has been considered a continuous process, mean expired alveolar CO $(\overline{F_{AE}})$ and mean alveolar CO ($\overline{F_A}$) are implicitly considered equal, and therefore aD′ is used rather than aD as discussed earlier. Furthermore, since all unevenness of ventilation and diffusion throughout the lung is ignored, aD′ is employed rather than D′. The solution of Equation *18* is

$$\overline{F_{AE}} = \frac{F_I}{1 + \frac{aD'PbC}{f(V_T - V_D)}}\left[1 - \exp\left(-\frac{t}{V_A} \times \left[f(V_T - V_D) + aD'PbC\right]\right)\right]. \quad (19)^{8}$$

E. *The Uptake of CO under "Steady State" Conditions over Long Time Periods*

If the circulation time of the blood is negligible in comparison with the period of time under consideration, then the body blood volume (B), which includes myoglobin, may be assumed mixed at any instant, and the washout time of the gas in the lungs can be neglected. If in addition, ventilation-perfusion and ventilation-diffusion ratios are assumed equal throughout the lung and ventilation is assumed a continuous process, then the change in total COHb content of the blood at any instant will equal the amount of CO diffusing across the pulmonary membrane. Stated symbolically,

$$\frac{dCOHb}{dt} B = \left[\overline{F_A} - \frac{COHbF_{cO_2}}{MO_2Hb}\right] aD'PbC. \quad (20)$$

The right hand term can be looked on as the pressure difference between the CO in the alveolar gas and that in the blood, multiplied by the pulmonary diffusing capacity, corrected for the slowness of the reaction of CO with Hb by the factor C. aD′ is used because the expired alveolar CO concentration is considered equal to the alveolar CO concentration in a continuous process, demanding a prime. Variations in diffusing capacity and ventilation throughout the lung have been ignored, demanding the "a." Because ventilation is continuous, the CO increase in the blood must equal the CO lost in the ventilatory exchange, or

$$\frac{dCOHb}{dt} B = f(V_T - V_D)(F_I - \overline{F_A}). \quad (21)$$

[8] Dr. Philip Hugh-Jones has told us that an equation similar in many respects to this one has been developed at the M.R.C. Pneumoconioses Unit in Wales, and will be reported in the future.

Equations *20* and *21* are combined and solved for $\overline{F_A}$ in terms of COHb. This value of $\overline{F_A}$ is then inserted in Equation *20* and the resulting differential form solved. The result is

$$COHb = \frac{F_I S}{F_I + \frac{F_{cO_2}}{M}} \times (1 - \exp(-xt + yCOHb)), \quad (22)$$

where

$$x = \frac{[aD'PbC + f(V_T - V_D)]\left(F_I + \frac{F_{cO_2}}{M}\right)^2}{BaD'PbCf(V_T - V_D)\left(\frac{F_{cO_2}}{M}\right)S},$$

$$y = \frac{\left(F_I + \frac{F_{cO_2}}{M}\right)}{S\frac{F_{cO_2}}{M}}$$

and S is the capacity of the blood for CO or O_2 in ml. gas (STPD) per ml. blood. Although this relationship is complicated it will describe satisfactorily the published data of Forbes, Sargent, and Roughton (7) and Pace, Consolazio, White, and Behnke (8). The equations of these investigators (7, 8) and of Hatch (11) can be shown to be approximate forms of Equation *22*. Even this complicated equation contains a number of simplifying assumptions, which are listed above, plus an additional assumption that C does not vary significantly during an experiment, which is probably true enough, provided the arterial blood is not unsaturated. This equation is useful, either to obtain estimates of aD′ or knowing aD′ and C, to predict the rate of build up of COHb in the blood. Variations in C are primarily a function of changes in the alveolar O_2 tension.

SUMMARY

Preliminary investigations on the Krogh CO method of measuring the diffusing capacity of the lung revealed the necessity for re-examining the theory of CO uptake from the lungs. Equations have been derived which describe mixed expired alveolar CO concentration, during breath-holding following a single inspiration of a gas containing CO and during "steady state" breathing of a mixture containing CO, when the alveoli have different ventilation rates, alveolar gas vol-

umes, and diffusing capacities. The effect of significant amounts of COHb in the mixed venous blood is discussed. Two equations are also derived describing the expired alveolar CO concentration during the breathing of a mixture containing CO. The first deals with the initial "washout" of the lung gases, and the attainment of the gas "steady state." The second deals with the much slower build-up of COHb in the mixed venous blood.

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