Theoretical Analyses for Arterial-Venous $O_2$ Content Difference and Haldane Effect during Rebreathing

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Abstract The Haldane effect coefficient in vivo and arterial-venous $O_2$ content difference ($a-v)C_{O_2}$) are, more or less, influenced by the contact time ($t_c$), $P_O_2$, and $P_CO_2$ differences between venous blood and alveolar air. To increase the accuracy of the ($a-v)C_{O_2}$ and the cardiac output measured by means of the rebreathing technique, factors to correct the Haldane effect ($F(H)$) and ($a-v)C_{O_2}$ ($F(avC_{O_2})$) were obtained theoretically from the numerical solutions of simultaneous $O_2$ and $CO_2$ diffusions in the red blood cell. Both the factors were complicated functions of $t_c$, the difference in $P_CO_2$ between venous blood and alveolar air, as well as ($a-v)C_{O_2}$. For simplicity, we eliminated $t_c$ from the above functions by using the standardized relation between the $t_c$ and ($a-v)C_{O_2}$ measured from a rebreathing experiment in man. The $F(H)$ was a linear function of ($a-v)C_{O_2}$. The ($a-v)C_{O_2}$ was calculated by dividing the product of $F(H)$ and the slope of the $CO_2$ dissociation curve by that of a gas exchange ratio against the $P_CO_2$ in rebreathing air. The $F(avC_{O_2})$ was given by a ratio of ($a-v)C_{O_2}$ at any alveolar $P_CO_2$ to the standard one, in which arterial blood has the same intracellular pH as that in venous blood. It was a linear function of the difference in $P_CO_2$ between venous blood and alveolar air, whose slope was inversely related to the ($a-v)C_{O_2}$ itself.

Key words: $O_2$ and $CO_2$ diffusion in RBC, Haldane effect, arterial-venous $O_2$ difference, $R-P_CO_2$ relation, contact time.

MOCHIZUKI and KAGAWA (1986) clarified that the coupled $O_2$ and $CO_2$ diffusions in the red blood cell (RBC) are not so fast, that the $CO_2$ equilibrium is hardly established between alveolar air and capillary blood during the contact time ($t_c$). The venous-arterial $CO_2$ content difference due to the Haldane effect ($(v-a)C_{CO_2}(H)$) has hitherto been expressed by multiplying the slope of the $CO_2$ dissociation curve ($z'$) by the difference between the true- and oxygenated-venous $P_CO_2$ ($oxP_CO_2- trP_CO_2$) (CHRISTIANSEN et al., 1914). Using this relation,
MOCHIZUKI et al. (1984) derived an equation to determine the arterial-venous O₂ content difference \((a-v)C_\text{O}_2\) from the \(\alpha'\) and the slope of a gas exchange ratio versus the \(P_{\text{CO}_2}\) in rebreathing air \((\theta)\), as given by \((a-v)C_\text{O}_2 = \alpha'/\theta\). When the CO₂ equilibrium is not reached, the \((v-a)C_\text{O}_2(H)\) becomes less than the product of \(\alpha' \cdot (\text{ox}P_{\text{CO}_2} - \text{tr}P_{\text{CO}_2})\). Accordingly, to obtain the \((a-v)C_\text{O}_2\) by dividing the \(\alpha'\) by \(\theta\), a correcting factor for the \(\alpha'/\theta\) is requisite. Moreover, the \((a-v)C_\text{O}_2\) depends on the alveolar \(P_{\text{CO}_2}\) \((P_{\text{ACO}_2})\) owing to the Bohr effect, whose reaction rate is not so fast as the blood flow through the capillary. Therefore, to precisely obtain the \((a-v)C_\text{O}_2\) during the rebreathing process, another factor to correct the \((a-v)C_\text{O}_2\) in respect to the \(P_{\text{ACO}_2}\) is indispensable. In the present study, we attempted to derive the above two correcting factors from the numerical solution of O₂ and CO₂ diffusions in the RBC.

The change in \((a-v)C_\text{O}_2\) caused by reducing the \(t_c\) from 0.7 to 0.4 s was about 7%. The change in \((a-v)C_\text{O}_2\) caused by changing the \(P_{\text{ACO}_2}\) by 10 Torr from the venous \(P_{\text{CO}_2}\), depending upon the \(t_c\), is in a range of 2 to 3% of the \((a-v)C_\text{O}_2\). Namely, the above changes are not significant compared with the errors arising in the measurements. However, to estimate the contact time from the CO₂ diffusion quantity in the RBC (MOCHIZUKI et al., 1987), such errors cannot be disregarded.

COMPUTATION OF \((a-v)C_\text{O}_2\) AND \((v-a)C_\text{CO}_2\)

The diffusivity of O₂ across the RBC boundary was expressed in terms of the transfer coefficient \((\eta(\text{O}_2))\), which was determined to be \(2.5 \times 10^{-6} \text{cm} \cdot \text{s}^{-1} \cdot \text{Torr}^{-1}\) by using a numerical solution of oxygenation equation (KAGAWA and MOCHIZUKI, 1982) by referring to the experimental data (MOCHIZUKI, 1966). The transfer coefficient of CO₂ \((\eta(\text{CO}_2))\) was also estimated from the numerical solution of the diffusion equation accompanying the \(\text{HCO}_3^-\) shift (KAGAWA and MOCHIZUKI, 1984), and from the experimental data on the CO₂ diffusion and \(\text{HCO}_3^-\) shift (NIIZEKI et al., 1983, 1984). It was determined to be \(2.5 \times 10^{-6} \text{cm} \cdot \text{s}^{-1} \cdot \text{Torr}^{-1}\) similar to the \(\eta(\text{O}_2)\). The transfer coefficient of \(\text{HCO}_3^-\) was \(5 \times 10^{-4}\) and \(7 \times 10^{-4} \text{cm} \cdot \text{s}^{-1}\) for the inward and outward shifts, respectively. Thus, using the above parameter values, we computed the O₂ and CO₂ diffusions into and out of the RBC in vivo. The diffusivity of CO₂ across the alveolar membrane was assumed to be so great as to be disregarded by referring to the following paper (MOCHIZUKI et al., 1987). However, the overall transfer coefficient of O₂ in vivo was taken to be equal to that of CO, \(1.7 \times 10^{-6} \text{cm} \cdot \text{s}^{-1} \cdot \text{Torr}^{-1}\) measured by UCHIDA et al. (1986). The changes in O₂ and CO₂ contents and intracellular tensions were computed along the contact time by changing the \(P_{\text{ACO}_2}\) at various venous \(P_{\text{CO}_2}\) and \((a-v)C_\text{O}_2\) levels according to the experimental conditions during rebreathing. For obtaining the correction factor for the Haldane effect, the actual venous \(P_{\text{CO}_2}\) must be distinguished from the oxygenated venous \(P_{\text{CO}_2}\) \((\text{ox}P_{\text{CO}_2})\). In the present paper, we designate the actual venous \(P_{\text{CO}_2}\) as the true venous \(P_{\text{CO}_2}\) \((\text{tr}P_{\text{CO}_2})\). The \((a-v)C_\text{O}_2\) was varied by changing the venous \(P_{\text{O}_2}\) \((P_{\text{VO}_2})\), whereas the alveolar \(P_{\text{O}_2}\) \((P_{\text{AO}_2})\) was
taken to be 90 Torr throughout the computation. For solving the differential equation for diffusions the same computer program as developed in the preceding papers was used (KAGAWA and MOCHIZUKI, 1982, 1984; KAGAWA, 1984).

In the previous paper (MOCHIZUKI and KAGAWA, 1986), the CO₂ dehydration rate in extracellular fluid was assumed to be 1.5 s in time constant, referring to the measured data of KLOCKE (1978). In the present study, however, the time constant was taken to be 0.1 s, referring to the data measured by BIDANI et al. (1983). From the O₂ and CO₂ diffusion equations, the diffusion rate factor of CO₂ ($F_c(CO_2)$: s⁻¹·Torr⁻¹) is calculated as

$$F_c(CO_2) = \frac{\Delta C_{CO_2}(t_c)}{\Delta P_{CO_2} \cdot t_c},$$

where $\Delta P_{CO_2}$ and $\Delta C_{CO_2}(t_c)$ are the time average of the $P_{CO_2}$ gradient across the RBC boundary and the CO₂ diffusion quantity during the contact time of $t_c$, respectively. Since the $F_c(CO_2)$ is distributed in a narrow range, MOCHIZUKI et al. (1987) attempted to derive the $t_c$ from the above equation. Their results showed that the $F_c(CO_2)$ depended on the extracellular HCO₃⁻ dehydration rate and, when the above rate was 0.1 s in time constant, the estimated contact time coincided well with that obtained from the CO diffusing capacity. Thus, in the present study the time constant of 0.1 s measured by BIDANI et al. (1983) was adopted for the extracellular HCO₃⁻ dehydration rate. Other parameters such as the CO₂ dissociation curve, the buffer value and the Donnan ratio were the same as before (MOCHIZUKI and KAGAWA, 1986).

During rebreathing in a closed system, the alveolar $P_{O_2}$ and $P_{CO_2}$ alter fairly rapidly. Therefore, to simulate the gas exchange profile during breathing, the boundary conditions for $P_{CO_2}$ and $P_{O_2}$ have to be varied according to the respiratory

![Graph](image)

**Fig. 1.** Change in O₂ saturation due to the oxygenation of the RBC. $P_{O_2}=30$, $P_{O_2}=90$, $trP_{CO_2}=50$ Torr, and the $P_{CO_2}$ was altered from 40 to 52 Torr.
frequency. However, in the present study the $P_{ACO2}$ and $P_{AO2}$ were taken to be constant during the contact time for the purpose of clarifying the $P_{CO2}$- and contact-time-dependencies of arteriovenous $O2$ difference and the Haldane effect.

An example of changes in $O2$ saturation ($SO2$, %) during an oxygenation reaction is shown in Fig. 1, where the ordinate is partly cut to expand the scale at a high $SO2$ range above 90%. The venous and alveolar $P_O2$ ($P_{VO2}$ and $P_{AO2}$) thereof were taken to be 30 and 90 Torr, respectively. The $trP_{CO2}$ was kept constant at 50 Torr, but the $P_{ACO2}$ was altered from 40 to 52 Torr stepwise. The oxygenation rate was fairly fast: Within a contact time of 0.35 s more than 97% of the change in $SO2$ was accomplished. Although the $\eta(O2)$ was taken to be $1.7 \times 10^{-6}$ cm$\cdot$s$^{-1}$$\cdot$Torr$^{-1}$, the oxygenation rate was similar to the experimental data in vitro (Mochizuki, 1966), where the $\eta(O2)$ was estimated to be $2.5 \times 10^{-6}$ cm$\cdot$s$^{-1}$$\cdot$Torr$^{-1}$. The $SO2$ at a later stage somewhat increased by virtue of the Bohr effect as the $P_{ACO2}$ was reduced. The change in $SO2$ per unit change in $P_{ACO2}$ ($\Delta SO2/\Delta P_{ACO2}$) was about 0.09% Torr$^{-1}$, diminishing as the contact time was reduced.

The changes in blood CO2 content computed along the contact time are shown in Fig. 2, where the initial and boundary conditions of $P_{O2}$ and $P_{CO2}$ used for computation were entirely the same as those in Fig. 1. In contrast to the oxygenation rate, the change in CO2 content ($\Delta C_{CO2}$) was slower: In 0.35 s, the diffusion proceeded only about 80%. The $C_{CO2}$ at $t_e=0$ showed differences among the individual examples, because the change in the extracellular dissolved CO2 content was subtracted from (or added to) the venous $C_{CO2}$ before computing the diffusion process according to the difference between $trP_{CO2}$ and $P_{ACO2}$. When the

![Fig. 2. Change in blood CO2 content during the outward CO2 diffusion accompanying oxygenation. $P_{VO2}=30$, $P_{AO2}=90$, $trP_{CO2}=50$ Torr, and $P_{ACO2}$ was altered from 40 to 52 Torr.](image)
PA\textsubscript{CO}_2 is lower than the trP\textsubscript{VCO}_2, the C\textsubscript{CO}_2 is reduced exponentially. As the PA\textsubscript{CO}_2 increases, the C\textsubscript{CO}_2 curve deviates from the exponential curve. Even when the PA\textsubscript{CO}_2 exceeds the trP\textsubscript{VCO}_2, for instance, at PA\textsubscript{CO}_2 = 52 Torr, CO\textsubscript{2} molecules diffuse out of the RBC against the initial uphill P\textsubscript{CO}_2 gradient across the RBC boundary due to the Haldane effect. In such a case, the C\textsubscript{CO}_2 profile shows an irregular fluctuation at the initial stage.

Next, from the S\textsubscript{O}_2 and C\textsubscript{CO}_2 changes, the (a-v)C\textsubscript{O}_2 and (v-a)C\textsubscript{CO}_2 were calculated along the contact time, where the O\textsubscript{2} capacity was taken to be 20 vol\%.

\[ P_{CO_2} \text{ DEPENDENCY OF (a-v)C}_O \]

The (a-v)C\textsubscript{O}_2 is influenced by the intracellular pH (pH\texttextsubscript{2}), which depends on the \( t_c \) and the trP\textsubscript{VCO}_2, as well as the PA\textsubscript{CO}_2. Figure 3A and B shows the P\textsubscript{CO}_2- and \( t_c \)-dependencies of (a-v)C\textsubscript{O}_2, respectively, where the abscissa is the difference between the trP\textsubscript{VCO}_2 and PA\textsubscript{CO}_2. First, the O\textsubscript{2} and C\textsubscript{CO}_2 profiles such as Figs. 1 and 2 were computed at 3 different trP\textsubscript{VCO}_2 of 45, 50, and 55 Torr, whereas the P\textsubscript{V}_O and PA\textsubscript{O}_2 were invariably 30 and 90 Torr, respectively. The (a-v)C\textsubscript{O}_2, shown in Fig. 3A was obtained at the constant \( t_c \) of 0.5 s, but in Fig. 3B it was obtained at three different \( t_c \) of 0.4, 0.5, and 0.7 s and at the constant trP\textsubscript{VCO}_2 of 50 Torr. The (a-v)C\textsubscript{O}_2 increases

\[ \text{Fig. 3. Relationship between (a-v)C}_O, computed by altering P}_O, from 30 to 90 Torr and the difference between trP\textsubscript{VCO}_2 and PA\textsubscript{CO}_2. A: trP\textsubscript{VCO}_2 was 45, 50, and 55 Torr, where \( t_c = 0.5 \) s. B: the \( t_c \) was 0.7, 0.5, and 0.4 s, where trP\textsubscript{VCO}_2 = 50 Torr.} \]
linearly with an increase in difference between trPVco2 and PAO2. The increase rate ranges between 0.013 and 0.014 vol%·Torr⁻¹, being almost independent of the (a-v)CO₂ and t_c. In general, the Bohr effect augments at a S_O₂ range around 50%. Thus, insofar as the PVO₂ is maintained constant, the higher the trPVCO₂, the lower the venous S_O₂. As a result, the (a-v)CO₂ increases with increasing trPVCO₂. The increase rate of (a-v)CO₂ versus trPVCO₂ (Fig. 3A) ranges from 0.065 to 0.07 vol%·Torr⁻¹, being much greater than the P_ACO₂-dependency of the (a-v)CO₂. In contrast to the P_CO₂-dependency, the t_c-dependency of (a-v)CO₂ is significantly small.

Hitherto, the Ó2 dissociation curve has been described by referring to the extracellular pH levels. However, in our previous computation (Mochizuki and Kagawa, 1986), the S_O₂ was treated as a function of the intracellular pH, (pHᵢ). Similarly, in the present study, the (a-v)CO₂ is expressed as a dependent variable of the pHᵢ. When the pHᵢ in arterial blood is equal to that in venous blood, namely, the change in pHᵢ (ΔpHᵢ) is zero, the (a-v)CO₂ is referred to as the standard (a-v)CO₂ ((a-v)CO₂*). Figure 4A and B shows the P_CO₂- and t_c-dependencies of the ΔpHᵢ. The ΔpHᵢ were obtained from the same computed data as Fig. 3A and B. The lines in Fig. 4A were obtained at three different trPVCO₂ of 45, 50, and 55 Torr and at the constant t_c of 0.5 s. The lines in Fig. 4B were obtained at 3 different t_c of 0.4, 0.5, and

Fig. 4. Relationship between the change in intracellular pH and the P_CO₂ difference between venous blood and alveolar air. A: trPVCO₂ was 45, 50, and 55 Torr, where t_c = 0.5 s. B: t_c = 0.7, 0.5, and 0.4 s, where trPVCO₂ = 50 Torr. PVO₂ and P_AO₂ are invariably 30 and 90 Torr, respectively.
ANALYSES OF ARTERIOVENOUS O₂ AND CO₂ DIFFERENCES

0.7 s, maintaining the trP₀₂ at 50 Torr. The ΔpHₑ was linearly related to the difference between trP₀₂ and PA₀₂, whereas the dependency of ΔpHₑ on tₑ was greater than that on the trP₀₂. Because of such complicated variation in ΔpHₑ, it was difficult to derive a general mathematical formula that included all the initial and boundary conditions.

For clarifying the PA₀₂-dependency of the (a-v)Co₂, the relations of the (a-v)Co₂ to the tₑ and trP₀₂ were standardized by referring to the experimental data of SHIBUYA et al. (1987). The tₑ thereof was given by the following hyperbolic equation as shown in Fig. 5A:

\[ tₑ = 4.86 \cdot (a-v)C₀₂ * - 1.025 \]  

The trP₀₂, as illustrated in Fig. 5B, was approximated by the following quadratic equation:

\[ trP₀₂ = 40.5 + 0.375 \cdot (a-v)C₀₂ * - 4 \]  

Figure 6 shows the (a-v)Co₂ computed by using the standard trP₀₂ of Eq. (2), at 6 different (a-v)Co₂* ranging from 4.7 to 11.3 vol%. The chain line shows the (a-v)Co₂* determined by referring to the ΔpHₑ of zero. From the data of Fig. 6, the
The ratio of (a-v)Co2/(a-v)Co2* which will be denoted by F(avCo2) was calculated. Figure 7 shows the F(avCo2) at four different (a-v)Co2*, where the abscissa is the difference between trPvco2 and PAco2, and the parameter is the (a-v)Co2*. The ratio of (a-v)Co2/(a-v)Co2* which will be denoted by F(avCo2) was calculated. Figure 7 shows the F(avCo2) at four different (a-v)Co2*, where the abscissa is the difference between trPvco2 and PAco2, and the parameter is the (a-v)Co2*. The ratio
is linearly related to the difference of \((\text{tr}P_{\text{vCO}_2} - P_{\text{A CO}_2})\), and the slope of the \(F(\text{avC}_2)\) is reduced as the \((\text{a-v})C_2\) increases. All the lines converge to the point of \((\text{tr}P_{\text{vCO}_2} - P_{\text{A CO}_2}) = -1.2\) Torr, where \(F(\text{avC}_2)\) equals 0.99. Within the computed \((\text{a-v})C_2\) range, the \(F(\text{avC}_2)\) is approximately expressed as

\[
F(\text{avC}_2) = \left( \frac{2.25}{(\text{a-v})C_2^*} - 0.09 \right) \frac{\text{tr}P_{\text{vCO}_2} - P_{\text{A CO}_2} + 1.2}{100} + 0.99. \tag{3}
\]

HALDANE EFFECT COEFFICIENT AND ITS CORRECTING FACTOR

The gas exchange ratio \((R)\) was then computed from such profiles as shown in Figs. 1 and 2, by dividing the \((\text{v-a})C_2\) by the \((\text{a-v})C_2\) along the contact time. Figure 8 shows an example of the \(R-P_{\text{CO}_2}\) relations at 5 \(t_c\) values of 0.3 to 0.8 s, where the \(P_{\text{vO}_2}\) and \(P_{\text{A O}_2}\) are 30 to 90 Torr, respectively, and the \(\text{tr}P_{\text{vCO}_2}\) is taken to be 50 Torr. The \(R-P_{\text{CO}_2}\) relation is almost linear, and its slope is reduced as the \(t_c\) is shortened. The \(R\) value at the \(\text{tr}P_{\text{vCO}_2}\), corresponding to the Haldane effect coefficient (HEC), is apparently smaller than that in vitro of 0.29 to 0.3 (Fig. 12), as shown in Fig. 9. The HEC values in Fig. 9 are illustrated at four \((\text{a-v})C_2^*\) levels of 6.4 to 11.3 vol\%. The HEC, depending upon both the \((\text{a-v})C_2^*\) and \(t_c\), is given by the following equation:

For \((\text{a-v})C_2^* \leq 6\) vol\%:

\[
\text{HEC} = 0.2845 - (0.033/t_c) + 0.0423 \cdot t_c - 0.0328 \cdot t_c^2, \tag{4a}
\]

**Fig. 8.** \(R-P_{\text{CO}_2}\) lines computed from the numerical solution of the overall \(O_2\) and \(CO_2\) diffusions in the RBC. \(t_c\) was varied from 0.3 to 0.8 s, where the \(\text{tr}P_{\text{vCO}_2} = 50\) Torr, \(P_{\text{vO}_2} = 30\) and \(P_{\text{A O}_2} = 90\) Torr.
and for \((a-v)C_{O_2}^* > 6\text{ vol}\%\):

\[
\text{HEC} = 0.2845 + 0.15 \cdot 10^{-2} \{(a-v)C_{O_2}^* - 6\} - (0.033/t_c) + 0.0423 - 0.0328 \cdot t_c^2. \tag{4b}
\]

Eqs. (4a) and (4b) state that the HEC increases hyperbolically with increasing \(t_c\) and linearly as the \((a-v)C_{O_2}^*\) increases within a range higher than 6 vol\%.

When developing the rebreathing technique to estimate the \((a-v)C_{O_2}\), Mochizuki et al. (1984) did not take into account its pH dependency. However, to increase the accuracy of the \((a-v)C_{O_2}\), the \((a-v)C_{O_2}^*\) rather than the \((a-v)C_{O_2}\) must be evaluated, because \(F(\text{av}C_{O_2})\) is obtainable only from the \((a-v)C_{O_2}^*\), as shown in Eq. (3). Thus, we attempted to derive a factor for correcting the Haldane effect \((F(H))\) for obtaining the \((a-v)C_{O_2}^*\) as follows:

\[(a-v)C_{O_2}^* = F(H) \cdot \frac{x'(P_{m_2})}{\theta}, \tag{5}\]

where \(P_{m_2}\) is the middle between the ox\(P_{CO_2}\) and tr\(P_{CO_2}\). In the computation of the \(R-P_{CO_2}\) lines of Fig. 8, the change in extracellular dissolved \(CO_2\) was excluded from the \((v-a)C_{CO_2}\), as already shown in Fig. 2. Denoting the slope of the \(R-P_{CO_2}\) line of Fig. 8 by \(\theta'\), the relation between \(\theta\) and \(\theta'\) may be approximated as follows (see APPENDIX):

\[\theta = \theta' + \frac{x'_p}{(a-v)C_{O_2}^*}. \tag{6}\]
where \( \alpha_p' \) is the CO\(_2\) solubility in the plasma compartment. By setting the \( \theta \) of Eq. (6) into Eq. (5) and rearranging it, the \( F(H) \) is given by

\[
F(H) = \frac{\theta' \cdot (a-v)C_{O_2}^* + \alpha_p'}{\alpha'(P_{m_2})}.
\]

Thus, \( F(H) \) was calculated, using \( \theta' \) and \( \alpha'(P_{m_2}) \) computed under 6 standardized relations between \( trP_{VCO_2} \) and \( P_{ACO_2} \) of Eq. (2). First, from such theoretical \( R-P_{CO_2} \) lines as shown in Fig. 8, the \( trP_{VCO_2} \) and \( oxP_{VCO_2} \) were obtained together with \( \theta' \) by taking \( R=HEC \) and \( R=0 \), respectively. Next, by setting the \( P_{m_2} \) into the following formula for the slope of the CO\(_2\) dissociation curve (Tazawa et al., 1983), \( \alpha'(P_{m_2}) \) was evaluated:

\[
\alpha'(P_{m_2}) = 3.962 \cdot P_{m_2}^{-0.5857}.
\]

Moreover, by inserting the \( (a-v)C_{O_2}^* \) into Eq. (7) together with \( \alpha'(P_{m_2}) \) and \( \theta' \), the \( F(H) \) was calculated.

Figure 10 shows the \( F(H) \) plotted against the \( t_c \), where the parameter is the \( (a-v)C_{O_2}^* \) in a range of 4.7 to 11.3 vol\%. As the \( (a-v)C_{O_2}^* \) increases, the difference between \( trP_{VCO_2} \) and \( oxP_{VCO_2} \) increases, decreasing the \( \alpha'(P_{m_2}) \) due to the characteristic of the CO\(_2\) dissociation curve. Thus, the \( F(H) \) computed from Eq. (7) increases.

![Figure 10](image-url)
with increasing $(a-v)C_{O_2}^*$. The open circles depicted on each $F(H)$ curve was determined by referring to the standardized relations between $t_c$ and $(a-v)C_{O_2}^*$ of Eq. (1). Figure 11 illustrates the $F(H)$ of these circles plotted against the $(a-v)C_{O_2}^*$, which is virtually approximated by a straight line as follows:

For $(a-v)C_{O_2}^* \leq 6.8$:

$$F(H) = 1.005 - 0.67 \times 10^{-3} (a-v)C_{O_2}^* - 4.9\right) , \quad (9a)$$

and for $(a-v)C_{O_2}^* > 6.8$:

$$F(H) = 1 - 0.96 \times 10^{-2} (a-v)C_{O_2}^* - 7.2\right) . \quad (9b)$$

The above equation suggests that the relation of $(a-v)C_{O_2} = a'/\theta$ derived by MOCHIZUKI et al. (1984) holds, insofar as the $(a-v)C_{O_2}^*$ is smaller than 7.2 vol%.

**DISCUSSION**

Hitherto, it has been believed that the CO$_2$ diffusion is completed during the $t_c$, and $(v-a)C_{CO_2}$ could be estimated from the $oxP_{CO_2}$ and $P_{ACO_2}$ referring to the CO$_2$ dissociation curve (FARHI et al., 1976; WAGNER, 1977). However, as shown in Fig. 2, the CO$_2$ content in arterial blood is not equilibrated with the $P_{ACO_2}$ even in normal subjects. Namely, it is greater than that equilibrated with the $P_{ACO_2}$ in vitro, lessening the $(v-a)C_{CO_2}$. Analogously, the HEC in vivo becomes smaller than the value measured in vitro. Using the relation between the $t_c$ and $(a-v)C_{O_2}^*$ of Eq. (1) and Fig. 5A, the $t_c$ can be eliminated from Eqs. (4a) and (4b), and the HEC is expressed simply by the following equation:

$$HEC = 0.294 - 0.57 \times 10^{-2} \cdot (a-v)C_{O_2}^* . \quad (10)$$
As already mentioned, the \( R-P_{CO_2} \) line in Fig. 8 was computed by excluding the change in extracellular dissolved CO\(_2\). The difference in \( R \) between \( trP_{CO_2} \) and \( oxP_{CO_2} \) is certainly reduced by neglecting the above CO\(_2\) change, but the \( R \) at \( trP_{CO_2} \) or the HEC may not be altered, since the extracellular dissolved CO\(_2\) remains unchanged insofar as the extracellular \( P_{CO_2} \) is invariable. Therefore, Eq. (10) may be valid independently of whether the change in extracellular CO\(_2\) is implied in the computation of the HEC or not.

In the indirect Fick's CO\(_2\) method for measuring the \( Q \), the \( P_{CO_2} \) component of the (v-a)\( C_{CO_2} \) has often been calculated by multiplying the slope of the CO\(_2\) dissociation curve by \( (trP_{CO_2} - P_{ACO_2}) \). The \( trP_{CO_2} \) thereof has been estimated by assuming the HEC as 0.32 (Kim et al., 1966). The CO\(_2\) diffusions curve used for computing the numerical solution of O\(_2\) and CO\(_2\) diffusions was cited from the measured data of Tazawa et al. (1983). As shown in Fig. 12A, the dissociation in CO\(_2\) content between oxygenated and deoxygenated blood, increases from 5.57 to 6.2 vol\(\%\), as the \( P_{CO_2} \) increases from 30 to 70 Torr. The HEC \textit{in vitro} calculated by dividing the above CO\(_2\) content difference by the O\(_2\) capacity, 20 vol\(\%\), is illustrated in Fig. 12B, which is about 0.3 in a \( P_{CO_2} \) range around 50 Torr. Therefore, it was impossible to expect a value higher than 0.3 for the HEC \textit{in vivo}. For practical

\[ fig. 12. \text{A: CO}_2\text{ dissociation curve of oxygenated and deoxygenated blood used for computing the numerical solution of O}_2\text{ and CO}_2\text{ diffusions in the RBC. B: Haldane effect coefficient } \textit{in vitro} \text{ obtained by dividing the CO}_2 \text{ content difference between the two dissociation curves in A by the O}_2 \text{ capacity of 20 vol}\%\text{.} \]
Equation (10) states that the HEC in vivo is distributed in a range of 0.22 to 0.26, when the $P_{A\text{O}_2}$ is around 100 Torr in the normal subjects at rest and during exercise. Therefore, when the $trP\text{vCO}_2$ is tentatively estimated by keeping the HEC in vivo to be invariably 0.28, $trP\text{vCO}_2$ may be underestimated. UCHIDA et al. (1986) measured $O_2$ and $CO_2$ concentrations in rebreathing air at rest and during exercise of about 1.3 l/min in $V_{O_2}$, and from the recorded $O_2$ and $CO_2$ curves they calculated the $\theta$ and further $(a\text{-}v)C_{O_2}^*$. The $\theta$ and $(a\text{-}v)C_{O_2}^*$ at rest were 0.064 Torr$^{-1}$ and 6.77 vol$\%$, on the average, and those during exercise were 0.034 Torr$^{-1}$ and 10.29 vol$\%$, respectively. By inserting the above $(a\text{-}v)C_{O_2}^*$ into Eq. (10), the HEC at rest and during exercise were estimated to be 0.255 and 0.235. Therefore, the difference between the assumed value, 0.28, and the above HEC value will be 0.025 and 0.045, respectively. By dividing these differences by the respective $\theta$ value, namely, 0.064 and 0.034 Torr$^{-1}$, the error caused by fixing the HEC at 0.28 is evaluated to be about 0.4 and 1.3 Torr, respectively.

The $F(\text{avCO}_2)$ of Eq. (3) and $F(H)$ of Eq. (7) were obtained by using the standardized relations of $P\text{vCO}_2$ and $t_e$ to the $(a\text{-}v)C_{O_2}^*$, namely, by using Eqs. (1) and (2), respectively. The above standardization was derived from the experimental data obtained at rest and during exercise in normal subjects (UCHIDA et al., 1986; SHIBUYA et al., 1987). Therefore, $F(\text{avCO}_2)$ and $F(H)$ may not be used, when the $P\text{vCO}_2$ and $t_e$ widely deviated from the normal relations given by Eqs. (1) and (2). Both the factors are close to the unity, and practically are not necessary for the purpose of estimating the $(a\text{-}v)C_{O_2}^*$ and the cardiac output. However, to evaluate the contact time from the diffusion quantity of $CO_2$ out of the RBC (MOCHIZUKI et al., 1987), such precise corrections become indispensable. For instance, when either $F(\text{avCO}_2)$ or $F(H)$ has an error of 0.01, the contact time receives an error of about 0.1 s or so. To derive such accurate correction factors seems to be impossible unless theoretical studies are made on the $O_2$ and $CO_2$ diffusion processes in the RBC.

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APPENDIX

Relation between two $R-P_{CO_2}$ lines computed with and without the change in extracellular dissolved $CO_2$. When the change in extracellular dissolved $CO_2$ ($\Delta C_{CO_2}(p)$) is excluded from the (v-a)$C_{CO_2}$, the slope of the computed $R-P_{CO_2}$ line ($\theta'$) becomes smaller than the experimental slope obtained by taking $\Delta C_{CO_2}(p)$ into account ($\theta$). For simplicity, let the former and latter $R-P_{CO_2}$ lines be $\theta'$ - and $\theta$ -lines, respectively. When the extracellular $P_{CO_2}$ remains unchanged, $\Delta C_{CO_2}(p)$ comes to nought, and therefore, both the $\theta$ and $\theta'$ lines intersect at the $trP_{CO_2}$. Thus, at the $oxP_{CO_2}'$, at which the $\theta$ -line becomes 0, the $R$ on the $\theta'$ -line is still higher than 0, as shown by symbol $\delta$ in Fig. 13. The $\Delta C_{CO_2}(p)$ caused by altering the $P_{CO_2}$ from $trP_{CO_2}$ to $oxP_{CO_2}'$ is given by $\Delta C_{CO_2}(p) = (oxP_{CO_2}' - trP_{CO_2})$. Hence, the $\delta$ will be given by
dividing $\alpha_p^{'}(\text{oxP}_\text{CO}_2 - \text{trP}_\text{CO}_2)$ by (a-v)$C_{O_2}$ which is evaluated at the ox$P\text{CO}_2$. As the $R$ at tr$P\text{CO}_2$ equals the HEC, the following relation will hold:

$$\text{HEC} = \theta'(\text{oxP}_\text{CO}_2 - \text{trP}_\text{CO}_2),$$

$$= \theta'(\text{oxP}_\text{CO}_2 - \text{trP}_\text{CO}_2) + \frac{\alpha_p^{'}}{(a-v)C_{O_2}^{*}}(\text{oxP}_\text{CO}_2 - \text{trP}_\text{CO}_2).$$

(11)

By eliminating $(\text{oxP}_\text{CO}_2 - \text{trP}_\text{CO}_2)$ from the above equation, we can obtain the following equation:

$$\theta = \theta' + \frac{\alpha_p^{'}}{(a-v)C_{O_2}^{*}}.$$  

(12)

Because the $(a-v)C_{O_2}$ at ox$P\text{CO}_2$ can be approximated by $(a-v)C_{O_2}^{*}$ within an error of a few $\%$, and in addition, the $\alpha_p^{'}$ is much smaller than $(a-v)C_{O_2}^{*}$, Eq. (12) may be rewritten as

$$\theta = \theta' + \frac{\alpha_p^{'}}{(a-v)C_{O_2}^{*}}.$$  

(6)