Analysis of Bicarbonate Concentration in Human Blood Plasma at Steady State in Vivo

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ABSTRACT

The bicarbonate concentration in plasma in vivo, \([\text{HCO}_3^-]\), has a \(P\text{CO}_2\)-dependent component, \([\text{HCO}_3^-]^{*}\), and a metabolic component, \([\text{HCO}_3^-]^o\). The \([\text{HCO}_3^-]^{*}\) in elderly patients and volunteers was expressed by an exponential function of \(P\text{CO}_2\) obtained by analysis of the venous-arterial (a-v) difference in \([\text{HCO}_3^-]\). The slope of \([\text{HCO}_3^-]^{*}\) against \(P\text{CO}_2\) was about 25% higher than that measured in oxygenated and deoxygenated blood in vitro. The regression functions of constituent ions were all linear versus \([\text{HCO}_3^-]^{*}\) and \([\text{HCO}_3^-]^o\) over the physiological \(P\text{CO}_2\) range. The relationship between \(P\text{CO}_2\) and \([\text{HCO}_3^-]^{*}\) agreed well with that calculated from the \(CO_2\) reaction rates on the active site of carbonic anhydrase using the Michaelis-Menten equation. At steady state the a-v difference in \([\text{HCO}_3^-]\) is proportional to that in \(O_2\) content (\([O_2]\)) as estimated from the respiratory quotient \((RQ)\). Thus, \([\text{HCO}_3^-]^{*}\) inevitably implied the Haldane effect component of \([\text{HCO}_3^-]^{HE}\) (\([\text{HCO}_3^-]^{HE}\)). However, \([\text{HCO}_3^-]^{HE}\) measured in oxygenated and deoxygenated blood was free from the change in \([O_2]\) or the Haldane effect. The relationship between \([\text{HCO}_3^-]^{HE}\) and \([\text{HCO}_3^-]^{*}\) could be evaluated from the in vivo and in vitro difference in \([\text{HCO}_3^-]\), and the effect of \(RQ\) on \([\text{HCO}_3^-]^{HE}\) was clarified. For analysing the ionic concentrations in plasma at steady state and the acid-base status, the equation for \([\text{HCO}_3^-]^{*}\) was considered indispensable.

Key words: Haldane effect of \([\text{HCO}_3^-]\), \(CO_2\) reaction rates, Carbonic anhydrase, Respiratory quotient, Strong ion difference

INTRODUCTION

The bicarbonate concentration \([\text{HCO}_3^-]\) in capillary blood changes in parallel with blood plasma is influenced by the changes in \(P\text{CO}_2\), \(O_2\) saturation \((SO_2)\) and the water content\(^{1}\). At steady state in vivo \(SO_2\) in

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[HCO$_3^-$], so that the respiratory quotient (RQ) is kept constant at a fixed level. When the O$_2$ changes due to the O$_2$ reactions in the red blood cell (RBC), CO$_2$ reacts with carbonic anhydrase and a change in [HCO$_3^-$] (i.e., the Haldane effect, HE) results$^2$. When HCO$_3^-$ in the RBC is dehydrated following a decrease in PCO$_2$ and an increase in SO$_2$, the bases K$^+$ and Na$^+$ are released from HCO$_3^-$ and conjugate with ionized buffer proteins. Since the buffer proteins are not as osmotically active as strong ions, the osmotic pressure in the RBC drops, causing a water shift from the RBC into plasma across the RBC membrane together with a Cl$^-$ shift$^{11,31,4}$.

When Cl$^-$ and water shift from the RBC into plasma across the RBC membrane$^6$, the concentration of constituent ions in plasma changes in parallel with [HCO$_3^-$]. Since the increase in [Cl$^-$] in plasma caused by the Cl$^-$ shift is countered by the opposite change in [Cl$^-$] due to the water shift, the change in [Cl$^-$] in plasma is minimized. However, since the RBC membrane is impermeable to Na$^+$, the [Na$^+$] changes greatly in inverse proportion to the change in water content. When HCO$_3^-$ is dehydrated in the lung capillaries by the increase in SO$_2$, the decrease in [Na$^+$] in plasma becomes greater than that in [Cl$^-$], and thus, the strong ion difference ([SID]) also decreases together with [HCO$_3^-$]$^6$. Hence, to confirm the accuracy of the measured [HCO$_3^-$], we examined the quantitative relationship between [HCO$_3^-$] and other ionic concentrations.

The [HCO$_3^-$] measured in plasma in vivo has a PCO$_2$-dependent component, [HCO$_3^-$]$^*$ and a metabolic component, [HCO$_3^-$]$^o$. The [HCO$_3^-$]$^*$ is mainly controlled by the kidney, but the response of the kidney to [HCO$_3^-$]$^*$ is so slow$^5$ that, when the arterial-venous (a-v) difference in [HCO$_3^-$] was measured, [HCO$_3^-$]$^*$ could be neglected, hence, [HCO$_3^-$]$^o$ could be approximated by an exponential function of PCO$_2$.$^7$

As is well known, the CO$_2$ reactions in blood are catalyzed by carbonic anhydrase (CA), which is present not only in the RBC, but also in the vascular endothelium$^{8-13}$. Hydration of CO$_2$ and dehydration of HCO$_3^-$ occur on the active site of CA$^{14,15}$. The CO$_2$ reaction rates obey the Michaelis-Menten equation, and the relationship between PCO$_2$ and [HCO$_3^-$] is defined by the balance between the dehydration and hydration rates at equilibrium. [HCO$_3^-$]$^*$ measured at steady state in vivo agreed well with that calculated from the CO$_2$ reaction rates. From this fact it was suggested that a small change in [HCO$_3^-$] in plasma caused by a change in SO$_2$ was corrected by interaction of the catalytic CO$_2$ reactions between CA in the RBC and that in the capillary endothelium.

In the present study, the ionic concentrations were all given by the linear combinations of [HCO$_3^-$]$^*$ and [HCO$_3^-$]$^o$. Further, electrical neutrality was maintained, regardless of the changes in [HCO$_3^-$]$^*$ and [HCO$_3^-$]$^o$. Even small changes in [HCO$_3^-$]$^*$ and [Na$^+$] caused by a shift of water across the RBC membrane could be precisely detected. Hence, it seemed justifiable to use [HCO$_3^-$]$^*$ as a criterion to analyze the acid-base balance in plasma at steady state.

**METHODS AND RESULTS**

1. **Analytical methods**

*Measuring procedure.* The relationship between constituent ions in plasma was analysed according to the following two steps. The first step was the determination of
[HCO₃⁻]⁺ and the second was the derivation of regression functions between [HCO₃⁻]⁺ and [HCO₃⁻]o and other ionic concentrations. The analysis was made in blood sampled from elderly patients and volunteers. The blood from the patients was obtained under the consent for testing the pulmonary functions and acid-base balance. Arterial blood was sampled from the femoral artery and venous from the median cubital vein. The ionic concentrations, [Na⁺], [K⁺] and [C⁻], were measured together with pH and P_CO₂ using a combined gas analyser (Ciba Corning 188). [H⁺] was calculated from pH, and [HCO₃⁻] from [H⁺] and P_CO₂ using the Henderson equation\(^\text{16}\). The strong ion difference, [SID], was obtained by subtracting [Cl⁻] from the sum of [Na⁺] and [K⁺]. The anion gap, [AG], was calculated by subtracting [HCO₃⁻] from [SID].

Mathematical treatment. The plots of all the ionic concentrations against P_CO₂, [HCO₃⁻]⁺ and [HCO₃⁻]o were analysed using the statistical method. The correlation coefficient and linear and quadratic regression functions were calculated with a MS-DOS computer program on a personal computer (NEC, PC-9801). Significance of the regression function was checked by the F-test using Stat-View program on a Macintosh computer.

The parameters used are tabulated in Table 5 together with the equations relating to other parameters.

2. Determination of [HCO₃⁻]⁺

[HCO₃⁻]⁺ \textit{in vivo} was determined in simultaneously taken samples (n=86) of venous and arterial blood from 56 elderly patients of both sexes. The summarized data on P_CO₂ and P_O₂ are shown in Table 1. The venous-arterial difference in [HCO₃⁻] [(HCO₃⁻) v - (HCO₃⁻) a] was linear against that in P_CO₂ (Pv_CO₂ - Pa_CO₂) as shown in Fig. 1, where the correlation coefficient was 0.954. The regression function was given as follows:

\[
[HCO₃⁻]_v - [HCO₃⁻]_a = 0.055 + 0.268 \times (Pv_CO₂ - Pa_CO₂), \text{ (mEq)}.
\]

The first term of Eq. (1), 0.055, was close to zero and the SD of deviations of individual points from the regression line was 0.43 mEq. This result indicated that [HCO₃⁻] is given by a linear combination of [HCO₃⁻]⁺ and [HCO₃⁻]⁻.

Table 1.

<table>
<thead>
<tr>
<th>No. of samples</th>
<th>No. of patients</th>
<th>Mean age ± SD</th>
<th>P_VO₂</th>
<th>P_O₂</th>
<th>P_VCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>16</td>
<td>83.5 ± 7.1</td>
<td>33.7 ± 12.9</td>
<td>71.0 ± 12.5</td>
<td>43.2 ± 5.5</td>
</tr>
<tr>
<td>61</td>
<td>40</td>
<td>84.2 ± 6.3</td>
<td>35.4 ± 11.9</td>
<td>71.3 ± 12.9</td>
<td>44.7 ± 3.6</td>
</tr>
</tbody>
</table>

Plasma Bicarbonate Concentration at Steady State
and that [HCO$_3^-$]$^*$ is evenly distributed irrespective whether venous or arterial blood, as reported by Forster.$^4$ With regard to the regression function, the following equation for [HCO$_3^-$]$^*$ has been tentatively suggested$^7$:

$$[\text{HCO}_3^-]^* = 4.75 \cdot \text{P}_{\text{CO}_2}^{0.455}, \text{ (mEq).}$$  \hspace{1cm} (2)

By setting the measured P$_{\text{CO}_2}$ into Eq. (2), [HCO$_3^-$]$^*$ was calculated and, to check its accuracy, [HCO$_3^-$]$^*$ was obtained by subtracting [HCO$_3^-$]$^*$ from the measured [HCO$_3^-$]. Furthermore, the regression function of the v-a difference in [HCO$_3^-$]$^*$ against that in P$_{\text{CO}_2}$ was examined. When Eq. (2) was used, the regression line approached the abscissa as shown in Fig. 2; the SD of the v-a difference in [HCO$_3^-$]$^*$ was 0.42 mEq. Thus, Eq. (2) was considered applicable for evaluating [HCO$_3^-$]$^*$.

When [HCO$_3^-$]$^*$ was obtained from Eq. (2), no significant difference in [HCO$_3^-$] was observed between venous and arterial blood. [HCO$_3^-$]$^*$ ranged from -5.83 to 13.84 mEq. The correlation coefficient of the arterial [HCO$_3^-$]$^*$ ([HCO$_3^-$]$^*$) against the venous [HCO$_3^-$]$^*$ ([HCO$_3^-$]$^*$) was 0.993 and the regression function was given by

$$[\text{HCO}_3^-]^* = 0.08 + 0.98 \cdot [\text{HCO}_3^-]^* \text{, (mEq).}$$  \hspace{1cm} (3)

In Fig. 3 [HCO$_3^-$]$^*$ measured in elderly normocarbic patients (Table 2A) are plotted against P$_{\text{CO}_2}$, where [HCO$_3^-$]$^*$ ranged from -0.7 to 0.7 mEq and [HCO$_3^-$]$^*$ from 21.0 to 30.4 mEq. The open circle indicates arterial blood and the closed circle venous blood. The correlation coefficient was 0.98, and the regression line was quadratic as shown by the solid line and approximated by the following exponential function:

$$[\text{HCO}_3^-]^* = 4.717 \cdot \text{P}_{\text{CO}_2}^{0.457}, \text{ (mEq).}$$  \hspace{1cm} (4)

The SD of deviations of individual points from the regression line was 0.43 mEq for both arterial and venous plasma.

When measured in tonometered blood, [HCO$_3^-$] in vitro depends on $\text{SO}_2$ as shown by the broken lines in Fig. 3. The upper curve shows [HCO$_3^-$] in deoxygenated blood and the
lower curve in oxygenated blood\(^{17}\). However, their slopes are independent of the change in \(\text{SO}_2\), and are less than that of \([\text{HCO}_3^-]^{*}\). Since the \(\text{SO}_2\) changes together with \([\text{HCO}_3^-]^{*}\) at steady state, the Haldane effect component of \([\text{HCO}_3^-]^{*}\) ([\(\text{HCO}_3^-\]) becomes dependent on \([\text{HCO}_3^-]^{*}\). Thus, by comparing the slope of \([\text{HCO}_3^-]^{*}\) with that of \([\text{HCO}_3^-]^{*}\), it became possible to obtain \([\text{HCO}_3^-]^{*}\). The arithmetic mean of \([\text{HCO}_3^-]^{*}\) in oxygenated and deoxygenated blood was used to provide a standard curve for \([\text{HCO}_3^-]^{*}\). Since the value of \([\text{HCO}_3^-]^{*}\) is dependent only on \(\text{PCO}_2\), it was designated by \([\text{HCO}_3^-]^{P}\) and was approximated from the measured values by the following equation \(^{17}\):

\[ [\text{HCO}_3^-]^{P} = 7.15 \cdot \text{PCO}_2^{0.345}, \text{ (mEq).} \] (5)

\([\text{HCO}_3^-]^{P}\) of Eq. (5) became equal to \([\text{HCO}_3^-]^{*}\) of Eq. (4) at \(\text{PCO}_2 = 41.01 \text{ mmHg}\) and \([\text{HCO}_3^-]^{*} = 25.75 \text{ mEq}\). For convenience, we took the origin of \([\text{HCO}_3^-]^{*}\) to be 25.75 mEq.

3. The relationship between ionic concentrations

The correlations between \([\text{HCO}_3^-]^{*}\), \([\text{HCO}_3^-]^{*}\) and other ionic concentrations were examined, using data on blood gas from a number of elderly patients and volunteers shown in Table 2A and B. The relationship between \([\text{HCO}_3^-]^{*}\) and other ionic concentrations was analysed in the group of normocarbic subjects in Table 2A. The \([\text{HCO}_3^-]^{*}\) ranged from -0.7 to 0.7 mEq and the \([\text{Na}^+]\) from 130 to 145 mEq. The concentrations measured are summarized in Table 3. There was no significant difference in parameter values between elderly patients and volunteers except for the SD of \([\text{HCO}_3^-]^{*}\). Since \([\text{HCO}_3^-]^{*}\) in the patients was limited within a narrower range, its SD was about half that in volunteers. In venous plasma \([\text{HCO}_3^-]\), \([\text{Na}^+]\) and \([\text{K}^+]\) were all significantly higher than in arterial plasma (\(P<0.01\)). No significant difference was observed in concentration of other ions between venous and arterial plasma.

The relationship between ionic concentra-

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**Table 2. Analysed blood samples**

A. Normocarbic subjects. \([\text{HCO}_3^-]^{*}\) ranged from 21.0 to 30.4 mEq.

<table>
<thead>
<tr>
<th>Elderly subjects</th>
<th>Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{HCO}_3^-]^{*}) (&gt; 0.7 &gt; [\text{HCO}_3^-] \rangle &gt; -0.7) (2.0 &gt; [\text{HCO}_3^-] \rangle &gt; -1.0)</td>
<td>(145 &gt; [\text{Na}^+] &gt; 130) (142 &gt; [\text{Na}^+] &gt; 136)</td>
</tr>
<tr>
<td>([\text{Na}^+]) (145 &gt; [\text{Na}^+] &gt; 130) (142 &gt; [\text{Na}^+] &gt; 136)</td>
<td>(29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>art. plasma</th>
<th>ven. plasma</th>
<th>ven. plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of samples</td>
<td>66</td>
<td>102</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>57</td>
<td>94</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>82.8 ± 6.8</td>
<td>82.7 ± 6.5</td>
</tr>
</tbody>
</table>

B. Normocapnic subjects. \([\text{HCO}_3^-]^{*}\) ranged from 23.75 to 27.75 mEq, and \([\text{Na}^+]\), from 130 to 145 mEq.

<table>
<thead>
<tr>
<th>Alkalosis</th>
<th>Volunter</th>
<th>Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{HCO}_3^-]^{<em>}) (15.2 &gt; [\text{HCO}_3^-]^{</em>} &gt; 2) (2.0 &gt; [\text{HCO}_3^-]^{<em>} &gt; 1.4) (2 &gt; [\text{HCO}_3^-]^{</em>} &gt; 8.7)</td>
<td>(41)</td>
<td>(29)</td>
</tr>
<tr>
<td>No. of samples</td>
<td>71</td>
<td>41</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Mean age SD</td>
<td>85.4 ± 6.0</td>
<td>35.9 ± 11.8</td>
</tr>
</tbody>
</table>

- ☑️-
Table 3. The mean and SD of ionic concentrations (mEq) measured in normocarbic subjects in Table 2A. #: statistically significantly different from the mean value of venous plasma (P<0.01). @: significantly different from SD in volunteers (P<0.01).

<table>
<thead>
<tr>
<th>Ions</th>
<th>Elderly patients</th>
<th>Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>[HCO₃⁻]</td>
<td>art. plasma 24.78 ± 1.24</td>
<td>ven. plasma 27.19 ± 1.57</td>
</tr>
<tr>
<td>[HCO₃⁻]</td>
<td></td>
<td>0.02 ± 0.42</td>
</tr>
<tr>
<td>[Na⁺]</td>
<td>136.23 ± 3.81</td>
<td>138.94 ± 3.09</td>
</tr>
<tr>
<td>[K⁺]</td>
<td>3.65 ± 0.39</td>
<td>3.84 ± 0.36</td>
</tr>
<tr>
<td>[Cl⁻]</td>
<td>101.18 ± 3.07</td>
<td>101.55 ± 2.41</td>
</tr>
<tr>
<td>[AG]</td>
<td>13.84 ± 1.51</td>
<td>14.04 ± 1.52</td>
</tr>
</tbody>
</table>

Table 4. The ionic concentrations in vivo (mEq) expressed by a linear combination of [HCO₃⁻]⁺ and [HCO₃⁻]⁻: [HCO₃⁻]⁺ = 4.717 PCO₂ \(1.85\), [HCO₃⁻]⁻ = [HCO₃⁻]⁺ \(1.52\) \[HCO₃⁻]⁻ \(25.75\) \(1.89\) \(+\) i[Na⁺]. The prefix ‘i’ indicates the concentration component independent of both [HCO₃⁻]⁺ and [HCO₃⁻]⁻.

\[\text{[Na⁺]} = 138.13 + 0.847 \cdot ([\text{HCO₃⁻}]⁺ \(25.75\) \(0.617\) \(\text{[HCO₃⁻]⁻} + i[\text{Na⁺}].\]
\[\text{[K⁺]} = 3.73 + 0.064 \cdot ([\text{HCO₃⁻}]⁺ \(25.75\) \(0.100\) \(\text{[HCO₃⁻]⁻} + i[\text{K⁺}].\]
\[\text{[Cl⁻]} = 101.93 \cdot 0.230 \cdot ([\text{HCO₃⁻}]⁺ \(25.75\) \(0.899\) \(\text{[HCO₃⁻]⁻} + i[\text{Cl⁻}].\]
\[\text{[AG]} = 14.18 \cdot 0.219 \cdot ([\text{HCO₃⁻}]⁺ \(25.75\) \(0.818\) \(\text{[HCO₃⁻]⁻} + i[\text{AG}].\]
\[\text{[SID]} = 39.93 + 0.781 \cdot ([\text{HCO₃⁻}]⁺ \(25.75\) \(0.182\) \(\text{[HCO₃⁻]⁻} + i[\text{SID}].\]

\[i[\text{AG]} = i[\text{SID}] = i[\text{Na⁺}] + i[\text{K⁺}] - i[\text{Cl⁻}].\]

The functions was evaluated from their regression functions against [HCO₃⁻]⁺ and [HCO₃⁻]⁻. The functions for [HCO₃⁻]⁺ were calculated for 212 normocarbic patients and volunteers (n = 244 samples) (Table 2A) and those against [HCO₃⁻]⁻ for 104 normocarbic (Table 2 B; n = 141 samples). The first and second terms of the equations shown in Table 4 are the regression functions against [HCO₃⁻]⁺. The components depending on [HCO₃⁻]⁺ were calculated by setting the [HCO₃⁻]⁺ obtained from Eq. (4) into the above regression functions. To determine the [HCO₃⁻]⁻-dependent component, the [HCO₃⁻]⁻-independent components were calculated by subtracting [HCO₃⁻]⁻-dependent components from their measured concentrations. Next, from the regression functions of the [HCO₃⁻]⁺-independent components against [HCO₃⁻]⁻, the [HCO₃⁻]⁺-dependent components were calculated. Finally, subtracting both the [HCO₃⁻]⁺ dependent and [HCO₃⁻]⁻-dependent components of each ion from its measured concentration, the completely independent component was obtained. The [HCO₃⁻]⁻-dependent and the independent components are shown by, respectively, the third and last terms of the experimental equations in Table 4, where the independent components are denoted by ‘i’.

To increase the accuracy of the regression function, the regression analysis was repeated after subtracting the relevant independent component from the measured concentration. Fig 4 shows the [Na⁺] plotted against [HCO₃⁻]⁻ for normocarbic subjects (Table 2B), where [Na⁺] was obtained by subtracting i[Na⁺] from the measured value. The correlation coefficient
was 0.981 and the regression coefficient was -0.617. As shown in Table 4, electrical neutrality is maintained in each component. From electroneutrality principle, $i_{AG}$ was equal to $i_{SID}$, and was distributed around 1.1 mEq and its SD was 3.09 mEq in all cases including hypernatremic and hyponatremic subjects.

4. Validation of the exponential function for $[\text{HCO}_3^-]$°

The relationship between the measured $[\text{HCO}_3^-]$° and P$_{\text{CO}_2}$ was compared with that calculated from the CO$_2$ reaction rates via carbonic anhydrase (CA). During CO$_2$ hydration the intermediate compound, H$^+$ - HCO$_3^-$, is first formed on the active site of CA, then the H$^+$ is exchanged for the conjugate bases. In kinetic studies, the rate of the second stage is so fast that the formation rate of the intermediate compound is considered identical to the CO$_2$ hydration rate. Thus, the formation rate of the intermediate compound can be calculated using the Michaelis-Menten equation as follows.

$$- \frac{d[\text{CO}_2]}{dt} = [\text{E}] \cdot K_{\text{cat}} \text{H}/(1 + K_{\text{cat}} \text{H}/[\text{CO}_2]),$$

(mM/sec$^{-1}$).

where [E] is the CA concentration per liter plasma, $K_{\text{cat}}$ (sec$^{-1}$), the turnover number for CO$_2$ hydration and $K_{\text{cat}}$H (mEq), the Michaelis constant of the hydration reaction. At equilibrium, the formation rate of the intermediate compound is countered by the reverse reaction rate. The reverse dissociation rate is considered to be proportional to the product of the activities of H$^+$ and HCO$_3^-$ of the intermediate compound. Let the mean of activity coefficients of H$^+$ and HCO$_3^-$ be F. The above product is approximated by multiplying F$^2$ by the product of [H$^+$] and [HCO$_3^-$]. Let the rate constant for the reverse dissociation reaction of the intermediate compound formation per liter plasma be $K_1$ (sec$^{-1}$ · mEq$^{-1}$). Since [H$^+$] of the intermediate compound is equal to [HCO$_3^-$], the following equation is derived at equilibrium:

$$K_{\text{cat}} \text{H}/(1 + K_{\text{cat}} \text{H}/[\text{CO}_2]) = K_1 \cdot F^2 \cdot [\text{HCO}_3^-]^2, \text{ (sec}^{-1}).$$

According to Pocker and Sarkanen, $K_{\text{cat}}$ is given by

$$K_{\text{cat}} \text{H} \ \equiv \ 10^{-5} = 6.73 + 0.633 \cdot (\text{pH} - 7.363), \text{ (sec}^{-1}).$$

In blood plasma in vivo, [H$^+$] is given from Eq. (4) and the Henderson equation as follows:

$$[\text{H}^+] = 5.187 \cdot 10^{-9} \cdot \text{PCO}_2^{0.543}, \text{ (M).}$$

Taking common logarithms of [H$^+$], pH is
given from Eq. (9) by

$$\text{pH} = 8.285 - 0.543 \cdot \log \text{PCO}_2. \quad (10)$$

According to Ohliger \cite{21}, $\_H$ is 15.0 mEq. [CO$_2$] is obtained by multiplying PCO$_2$ by CO$_2$ solubility 0.0308 mM mmHg$^{-1}$. Thus, using Eqs. (8) and (10), the hydration rate (Eq. 7) is numerically given by

$$\frac{\_H}{(1 + \frac{\_H}{[\text{CO}_2]})} = \frac{0.182}{10^4} \cdot \text{PCO}_2^{0.047}. \quad (11)$$

From Eqs. (7) and (11) [HCO$_3^-$] of the intermediate compound is given by

$$[\text{HCO}_3^-] = 0.427 \cdot 10^{-7} \cdot \text{PCO}_2^{0.452} / \sqrt{K_i \cdot F}. \quad (12)$$

Assuming that at the active site the buffer capacity is large enough and [SID] is variable enough to follow the CO$_2$ reactions, the coefficient, $\sqrt{K_i \cdot F}$, was evaluated by setting [HCO$_3^-$] and PCO$_2$ at the origin into Eq. (12). Since PCO$_2$ at the origin is 41.01 mmHg and [HCO$_3^-$]* 25.75 mEq, the coefficient, $\sqrt{K_i \cdot F}$ and the [HCO$_3^-$] were obtained as follows:

$$\frac{\_D}{(1 + \frac{\_D}{[\text{HCO}_3^-]})} = \frac{\_H}{(1 + \frac{\_H}{[\text{CO}_2]})}, \quad (15)$$

According to Ohliger \cite{21}, $\_D$ is 21.5 mEq, and [HCO$_3^-$] in plasma is given by Eq. (14). Hence, $\_D$ was numerically given by

$$\frac{\_D}{10^{-4}} = 0.756 \cdot \text{PCO}_2^{0.685}, (\text{sec}^{-1}). \quad (16)$$

Figure 5 shows $\_D$ of Eq. (16) together with $\_H$ of Eq. (8). These values agree well with those reported by Pocker and Sarkanen \cite{20}. This result suggests that Eq. (4) is applicable as the standard function of [HCO$_3^-$] irrespective of whether the blood is arterial or venous.

5. The difference between [HCO$_3^-$]* and [HCO$_3^-$]$_p$

The standard curve for [HCO$_3^-$]$_p$, given by Eq. (5), was approximated by the following equation:

$$[\text{HCO}_3^-] = 0.756 \cdot \text{PCO}_2^{0.685}, (\text{mEq}). \quad (17)$$
The difference between $[\text{HCO}_3^-]^* \text{ and } [\text{HCO}_3^-]$ corresponds to the Haldane effect component of $[\text{HCO}_3^-]$ ($[\text{HCO}_3^-]$ HE) and is given from Eq. (17) by

$$[\text{HCO}_3^-]_{\text{HE}} = 0.252 \cdot ([\text{HCO}_3^-]^* - 25.75), \text{ (mEq)}.$$  (18)

Eq. (18) suggests that the change in $[\text{HCO}_3^-]$ in vivo due to the Haldane effect is 25% of the change in $[\text{HCO}_3^-]^*$. When $[\text{HCO}_3^-]$ of venous blood is dehydrated in the capillary at $P_{\text{CO}_2}$, the a-v difference in $[\text{HCO}_3^-]_{\text{HE}}$ ($a\nu [\text{HCO}_3^-]_{\text{HE}}$) is evaluated from Eq. (18) by translating the origin of $[\text{HCO}_3^-]^*$ from 25.75 mEq to $[\text{HCO}_3^-]$, as given by

$$a\nu [\text{HCO}_3^-]_{\text{HE}} = 0.252 \cdot a\nu [\text{HCO}_3^-]^*, \text{ (mEq)},$$  (19)

where $a\nu [\text{HCO}_3^-]^*$ is the a-v difference in $[\text{HCO}_3^-]^*$. When $\text{HCO}_3^-$ is dehydrated in the RBC, a change in water content occurs in plasma\(^{1,4}\). The hematocrit (Hct) in tonometered blood has been measured previously over the $P_{\text{CO}_2}$ range of 10 to 90 mmHg\(^{17}\). The plasma volume in blood (1 - Hct) was approximated by the following:

$$1 - \text{Hct} = 0.544 - 0.906 \times 10^{-3} ([\text{HCO}_3^-]^* - 25.75).$$  (20)

Dividing both sides of the above equation by 0.544, the relative water content in plasma, which depends only on the $P_{\text{CO}_2}$ ($[\text{H}_2\text{O}]_p$) is given by

$$[\text{H}_2\text{O}]_p = 1.0 - 1.665 \times 10^{-3} ([\text{HCO}_3^-]^* - 25.75).$$  (21)

Fig 6 shows $[\text{Na}^+]$ in vivo ($[\text{Na}^+]^*$) plotted against $[\text{HCO}_3^-]$*, where $[\text{Na}^+]$ is the value obtained by subtracting its independent component, i[Na*], from the measured value. The unfilled circles indicate arterial blood and the filled circles venous blood. The correlation coefficient was 0.95 and the regression function was given by

$$[\text{Na}^+]^* = 138.13 + 0.487 \cdot ([\text{HCO}_3^-]^* - 25.75), \text{ (mEq)}.$$  (22)

In the plasma, when no change in $S_{\text{O}_2}$ occurs, $[\text{Na}^+]$ is obtained by dividing its concentration at the origin ($([\text{HCO}_3^-]^* = 25.75 \text{ mEq}$ by $[\text{H}_2\text{O}]_p$ of Eq. (21). Assuming $[\text{Na}^+]$ at the origin to be 138.13 mEq similar to $[\text{Na}^+]^*$, the relationship of $[\text{Na}^+]$ in the above plasma, denoted by $[\text{Na}^+]_p$, to $[\text{HCO}_3^-]^*$ is approximately given by the following:

$$[\text{Na}^+]_p = 138.13 + 0.232 \cdot ([\text{HCO}_3^-]^* - 25.75), \text{ (mEq)}.$$  (23)
Subtracting [Na’] of Eq. (23) from [Na’]* of Eq. (22), the change in [Na’] due to the change in So₂ (the Haldane effect), [Na’]HE is derived similarly to Eq. (19) as:

\[ [\text{Na’}]_{HE} = 0.255 \cdot [\text{HCO}_3^-]^*, \text{ (mEq).} \quad (24) \]

From Eqs. (19) and (24), it is clear that [Na’]HE agrees well with [HCO₃⁻]HE. Since [Na’] - [HCO₃⁻] = [Cl⁻] + [AG] - [K⁺], the above result indicates that, when So₂ changes, the sum of the changes in [Cl⁻] and [AG] is countered by that in [K⁺]. In plasma [K⁺] is only 2.7% of [Na’], hence, the change in [Cl⁻] and [AG] caused by the Haldane effect will be of the same magnitude as that in [K⁺]. From this result it is clear that the change in [SID] in plasma due to the Haldane effect is determined by that in [HCO₃⁻]*, which is controlled by the CO₂ reactions on the active site of CA in the capillary endothelium.

6. The Haldane effect component of [HCO₃⁻] at steady state

When venous blood enters the lung capillaries, HCO₃⁻ is dehydrated by a decrease in PCO₂ and an increase in So₂. Let the a-v difference in [HCO₃⁻] caused by the decrease in PCO₂ be [HCO₃⁻]p, and that due to the rise in So₂ (the Haldane effect) be [HCO₃⁻]HE. The sum of [HCO₃⁻]p and [HCO₃⁻]HE is the a-v difference in [HCO₃⁻]* (\[\text{HCO}_3^-\]^*). As realized from Eq. (14), [HCO₃⁻]* is defined by the CO₂ reactions on the active site of CA, and is given by the exponential equation of PCO₂ (Eq. 4). As shown in Eq. (17), [HCO₃⁻]p is linearly related to [HCO₃⁻]*. Thus, the difference \[ [\text{HCO}_3^-]^* \] - \[ [\text{HCO}_3^-]_p \] \[ [\text{HCO}_3^-]_{HE} \] must be proportional to \[ [\text{HCO}_3^-]^* \]. In other words, the ratio \[ [\text{HCO}_3^-]_{HE} / [\text{HCO}_3^-]^* \] must become constant (0.252) as shown in Eq. (19).

Since \[ [\text{HCO}_3^-]_{HE} \] is the difference in [HCO₃⁻] between oxygenated and deoxygenated blood and \[ [\text{HCO}_3^-]^* \] is obtained by multiplying \[ [\text{HCO}_3^-]_{HE} \] by the a-v difference in So₂ (\[ \text{So}_2 \]), we attempted to calculate the ratio \[ [\text{So}_2] / [\text{HCO}_3^-]^* \] with reference to the RQ.

The \[ [\text{So}_2] \] is obtained by dividing the a-v difference in O₂ content (\[ \text{O}_2 \]) by the O₂ capacity (CapO₂ = 8.985 mM). The ratio of the a-v difference in CO₂ content (\[ \text{CO}_2 \]) to \[ \text{O}_2 \] is the RQ. Denoting the Haldane effect component of \[ \text{CO}_2 \] by \[ \text{CO}_2_{HE} \], the a-v difference of it (\[ \text{CO}_2\]HE) is given by multiplying \[ \text{CO}_2_{HE} \] by \[ \text{So}_2 \]. The a-v difference in PCO₂-dependent component of \[ \text{CO}_2 \] (\[ \text{CO}_2\]p) is then obtained by subtracting \[ \text{CO}_2_{HE} \] from \[ \text{CO}_2 \], as follows:

\[ [\text{CO}_2]\]p = (RQ \cdot \text{CapO}_2 - [\text{CO}_2]_{HE}) \cdot (\text{ - }) \cdot [\text{So}_2]. \quad (25) \]

According to our previous measurement on \[ \text{CO}_2\]p in oxygenated blood\(^{17}\), the ratio \[ \text{CO}_2\]p/\[ \text{CO}_3^-\]* was 0.728 (mM in blood per mEq in plasma). Thus, from Eq. (25) the following equation is derived:

\[ \text{Fig. 7.} \]

[\text{HCO}_3^-]_{HE} calculated from Eq. (25) (solid line) and the ratio \[ [\text{So}_2] / [\text{HCO}_3^-]^* \] of Eq. (26) (broken line) plotted against the respiratory quotient (RQ). The arrow shows the values at RQ=0.9.
In Fig. 7, the solid line shows $[\text{HCO}_3^-]$ plotted against RQ, the broken line the ratio $[\text{SO}_3^2^-]/[\text{HCO}_3^-]$ and the arrow shows those values at RQ=0.9. $[\text{HCO}_3^-]$ measured was 1.88 mEq and agreed with the value obtained from Eq. (29) using RQ=0.9, suggesting that $[\text{HCO}_3^-]$ measured in blood with RQ=0.9. $[\text{CO}_2]$ measured was 2.65 mM. Setting this value in Eq. (26), $[\text{SO}_3^2^-]/[\text{HCO}_3^-]$ became 0.134, and the ratio $[\text{HCO}_3^-]_{HE}/[\text{HCO}_3^-]$ became 0.252, as given by Eq. (19). According to Eq. (29) it was suggested that $[\text{HCO}_3^-]_{HE}$ would be proportional to the RQ and the ratio $[\text{HCO}_3^-]_{HE}/[\text{HCO}_3^-]$ became constant, since the ratio $[\text{SO}_3^2^-]/[\text{HCO}_3^-]$ was inversely proportional to the RQ. If the dehydration rate of $\text{HCO}_3^-$ due to the oxygenation were increased in blood with a low RQ, $[\text{HCO}_3^-]$ in plasma could possibly become lower than $[\text{HCO}_3^-]$ due to an excess shift of water and $\text{HCO}_3^-$ across the RBC membrane. The $[\text{HCO}_3^-]$ is defined by the balance of the CO hydration and the dehydration of $\text{HCO}_3^-$ on the active site of CA in the capillary endothelium. Thus, the deficit in $[\text{HCO}_3^-]$ will be recovered by the CO$_2$ hydration to keep $[\text{HCO}_3^-]$ at the level of $[\text{HCO}_3^-]$. When $[\text{HCO}_3^-]$ in plasma exceeds $[\text{HCO}_3^-]$ by the deoxygenation of the RBC, the rise in $[\text{HCO}_3^-]$ will be limited by the dehydration reaction of $\text{HCO}_3^-$. At all event, the CO$_2$ reactions in the RBC due to the Haldane effect will interact on the catalytic reactions via CA in the capillary endothelium. Thus, the ratio $[\text{HCO}_3^-]_{HE}/[\text{HCO}_3^-]$ at steady state always becomes constant (0.252) regardless of the change in RQ, as shown in Eq. (19).

### 7. Relationship between $[\text{HCO}_3^-]$ and other ionic concentrations

The ionic concentrations accompanying the change in $[\text{HCO}_3^-]$ are also tabulated in Table 4. Depending on $[\text{HCO}_3^-]$, $[\text{Na}^+]$ and $[\text{K}^+]$ always change together with $[\text{Cl}^-]$. Thus, their changes are unrelated to the change in SID. However, the regression coefficient of $[\text{Na}^+]$ versus $[\text{HCO}_3^-]$ was -0.899 and the of the sum of $[\text{Na}^+]$ and $[\text{K}^+]$ versus $[\text{HCO}_3^-]$ was -
The above difference in $\text{SID}$ against $[\text{HCO}_3^-]$ was 0.182. This figure indicates that in the alkalotic plasma the deficit in $[\text{Cl}^-]$, $-0.182 \cdot [\text{HCO}_3^-]$, occurs as $[\text{HCO}_3^-]$ rises above zero, and that Na$^+$ and K$^+$ ions released from $\text{Cl}^-$ react with $\text{HCO}_3^-$, to maintain electroneutrality. In the acidoic plasma there are a deficit in $[\text{HCO}_3^-]$ and an excess in $[\text{Cl}^-]$, where the bases liberated from $\text{HCO}_3^-$ ions react with the $\text{Cl}^-$. On the other hand, the of $[\text{AG}]$ versus $[\text{HCO}_3^-]$, $-0.818$, was much greater than that of $[\text{SID}]$.

Theoretically, $[\text{AG}]$ should not be negative, and a negative value means the presence of some exogenous cations. Thus, in the alkalotic plasma, where $[\text{HCO}_3^-]^+ > 0$, a negative value of the $[\text{AG}]$ indicates that some exogenous cations are present. Fig. 8 shows the size of the change in concentration of the ions accompanying the change in $[\text{HCO}_3^-]^+$. All the changes in alkalotic plasma are shown in upper half of Fig. 8 and the presence of exogenous cations is designated by $[\text{AG}]_{\text{ExC}}$. The increase in concentration of these cations is balanced by the increase in $[\text{HCO}_3^-]^+$ to maintain electrical neutrality. When $[\text{HCO}_3^-]^+$ is zero, all the changes become zero, turning negative as $[\text{HCO}_3^-]^+$ becomes negative, as shown in lower half of Fig. 8. All the quantities are linearly and uniformly related to the change in $[\text{HCO}_3^-]^+$. In acidoic plasma, when $[\text{HCO}_3^-]^+ < 0$, the concentration of exogenous anions, denoted by $[\text{AG}]_{\text{ExA}}$, increases inversely as $[\text{HCO}_3^-]^+$ decreases. Depending on the decrease in $[\text{HCO}_3^-]^+$ the conjugate bases move from $\text{HCO}_3^-$ to the exogenous anions and electrical neutrality is maintained.

### DISCUSSION

The regression function of $[\text{HCO}_3^-]$ against $P\text{CO}_2$ measured in tonometered blood was greatly different from that measured at steady state. Since $S\text{O}_2$ in capillary blood changes in parallel with $[\text{HCO}_3^-]$, the Haldane effect component of $[\text{HCO}_3^-]$ ([HCO$_3^-$]$_{HE}$) is usually implied in $[\text{HCO}_3^-]^+$, as shown by Eq. (18). Furthermore, since the relationship between $P\text{CO}_2$ and $[\text{HCO}_3^-]^+$ is controlled by the activity of carbonic anhydrase, the $\text{av}[\text{HCO}_3^-]_{\text{HE}}$ turns proportional to $[\text{HCO}_3^-]^+$ as given by Eq. (19) and $[\text{HCO}_3^-]_{\text{HE}}$ also becomes proportional to the respiratory quotient as shown in Eq. (29). This well controlled relationship appears attributable to the interactive catalytic reactions between the active site of CA in the RBC and that in the capillary endothelium.

The $[\text{AG}]$ measured in plasma of normocar- bnic subjects is shown in Fig. 9, where $[\text{AG}]$ is the value obtained by subtracting its independent component $i[\text{AG}]$ from the measured value. The correlation coefficient was 0.774 and the regression function was given by

![Fig. 8](image-url)

The size of the change in concentration of constituent ions accompanying the change in $[\text{HCO}_3^-]^+$, obtained from Table 4. The change in $[\text{AG}]$ in alkalotic plasma is shown with $[\text{AG}]_{\text{ExC}}$ and that in acidoic plasma with $[\text{AG}]_{\text{ExA}}$. 

- [Sid] against [HCO$_3^-$] was 0.182. This figure indicates that in the alkalotic plasma the deficit in [Cl$^-$], $-0.182 \cdot [\text{HCO}_3^-]$, occurs as [HCO$_3^-$] rises above zero, and that Na$^+$ and K$^+$ ions released from Cl$^-$ react with HCO$_3^-$, to maintain electroneutrality. In the acidoic plasma there are a deficit in [HCO$_3^-$] and an excess in [Cl$^-$], where the bases liberated from HCO$_3^-$ ions react with the Cl$^-$. On the other hand, the of [AG] versus [HCO$_3^-$], $-0.818$, was much greater than that of [SID].
Plasma Bicarbonate Concentration at Steady State

\[ [\text{AG}] = 14.18 - 0.219 ([\text{HCO}_3^-]^*) - 25.75, \text{(mEq)} \]  
(31)

Hitherto, the concentration of ionized buffer proteins in plasma, [AG], has been considered to depend on pH\(^1\)\(^6\). However, as shown in Eq. (31), it was linearly related to \([\text{HCO}_3^-]^*\). This suggested that the conjugation of the ionized buffer proteins with \(\text{H}^+\) proceeds via the intermediate compound on the carbonic anhydrase. \([\text{H}^+]\) of the intermediate compound is equal to \([\text{HCO}_3^-]^*\) as given by Eq. (14). Let the concentration of unionized buffer proteins be [HAG] and the sum of [AG] and [HAG] be \([A_{\text{tot}}]\), and let the dissociation constant for \(\text{H}^+\) from combination with the buffer proteins be \(K_a\) (mEq). From the law of mass action the following equation is derived\(^\text{22}\):

\[ [\text{H}^+] \cdot [\text{AG}] = K_a \cdot ([A_{\text{tot}}] - [\text{AG}]). \]  
(32)

Assuming \([\text{H}^+]\) to be identical to \([\text{HCO}_3^-]^*\), this

is obtained from Eq. (14) and [AG] from Eq. (31), and the \([\text{H}^+] \cdot [\text{AG}]\) is numerically calculated. Fig. 10 shows the linear relationship between \([\text{H}^+] \cdot [\text{AG}]\) and [AG]. From the slope of the declining line in Fig. 10, \(K_a\) and \([A_{\text{tot}}]\) were calculated as follows:

\[ [\text{H}^+] \cdot [\text{AG}] = 32.08 \cdot 10^{-3} \cdot (25.55 \cdot 10^{-3} - [\text{AG}]). \]  
(33)

\([\text{H}^+]\) in Eq. (33) is that of the intermediate compound on the carbonic anhydrase and independent of pH in plasma relating to a change in \(\text{S}_\text{O}_2\), hence, the change in [AG] can be ignored in considering the Haldane effect. From the electroneutrality rule, \([\text{HCO}_3^-] = [\text{SID}] - [\text{AG}]\), hence, \([\text{HCO}_3^-]_{\text{IR}}\) becomes equal to the Haldane effect component of [SID]. When \([\text{HCO}_3^-]\) in plasma is equilibrated with that in interstitial fluid surrounding the capillaries, no difference in [SID] will occur across the capillary\(^\text{26}\).

When a \(\text{CO}_2\) gas mixture is inhaled, the \(\text{CO}_2\) hydration due to the rise in \(\text{PCO}_2\) and the dehydration of \(\text{HCO}_3^-\) due to the rise in \(\text{SO}_2\)
Table 5: Table of symbols and notations. The a-v difference denotes the arterial-venous difference.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>concentration of ionized buffer proteins in plasma</td>
</tr>
<tr>
<td>AG_lac</td>
<td>concentration of exogenous cations in plasma</td>
</tr>
<tr>
<td>AG_lac</td>
<td>concentration of exogenous anions in plasma</td>
</tr>
<tr>
<td>RQ_avCO _2</td>
<td>( RQ \cdot \text{av}[O_2] ): a-v CO(_2) content difference in vivo</td>
</tr>
<tr>
<td>( \alpha [CO_2] )</td>
<td>Haldane effect component of ( \alpha [CO_2] )</td>
</tr>
<tr>
<td>( \alpha [CO_2]^* )</td>
<td>CO(_2)_dependent component of ( \alpha [CO_2] )</td>
</tr>
<tr>
<td>( \alpha [HCO_3^-] )</td>
<td>a-v difference in [HCO(_3)_]</td>
</tr>
<tr>
<td>( \alpha [HCO_3^-]^* )</td>
<td>Haldane effect component of ( \alpha [HCO_3^-] )</td>
</tr>
<tr>
<td>( \alpha [Na^+] )</td>
<td>a-v difference in [Na(^+)]</td>
</tr>
<tr>
<td>( [CO_2] )</td>
<td>CO(_2) content in blood in vivo</td>
</tr>
<tr>
<td>( [CO_2]_P )</td>
<td>CO(_2) measured in oxygenated blood in vitro</td>
</tr>
<tr>
<td>CA</td>
<td>carbonic anhydrase</td>
</tr>
<tr>
<td>CapO</td>
<td>O(_2) capacity (8.985 mmol)</td>
</tr>
<tr>
<td>( E )</td>
<td>effective CA concentration in blood plasma</td>
</tr>
<tr>
<td>F</td>
<td>mean activity coefficient of [H(^+)] and [HCO(_3)_] on CA</td>
</tr>
<tr>
<td>HAG</td>
<td>concentration of un-ionized buffer proteins</td>
</tr>
<tr>
<td>Hct</td>
<td>hematocrit</td>
</tr>
<tr>
<td>( [HCO_3^-] )</td>
<td>measured value of [HCO(_3)_] in blood in vivo</td>
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<tr>
<td>( [HCO_3^-]_A )</td>
<td>[HCO(_3)_] in arterial blood</td>
</tr>
<tr>
<td>( [HCO_3^-]_V )</td>
<td>[HCO(_3)_] in venous blood</td>
</tr>
<tr>
<td>( [HCO_3^-]_m )</td>
<td>4.717 * PCO(_2)(^{0.657}): respiratory component of [HCO(_3)_]</td>
</tr>
<tr>
<td>( [HCO_3^-]^* )</td>
<td>metabolic component of [HCO(_3)_]</td>
</tr>
<tr>
<td>( [HCO_3^-]^* )</td>
<td>in arterial blood</td>
</tr>
<tr>
<td>( [HCO_3^-]^* )</td>
<td>in venous blood</td>
</tr>
<tr>
<td>( [HCO_3^-]_B )</td>
<td>2.09 * RQ: Haldane effect component in [HCO(_3)_]</td>
</tr>
<tr>
<td>( [HCO_3^-]^* )</td>
<td>PCO(_2)-dependent component of [HCO(_3)_]</td>
</tr>
<tr>
<td>( [H_2]O )</td>
<td>water content in plasma in tonometered blood with S(_O_2) = 0.5</td>
</tr>
<tr>
<td>( K_r )</td>
<td>rate constant of the dissociation of intermediate compound of CA</td>
</tr>
<tr>
<td>( K_s )</td>
<td>dissociation constant of H(^+) from combination with buffer proteins</td>
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<tr>
<td>K_inH</td>
<td>turnover number of CO(_2) hydration reaction via CA</td>
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<tr>
<td>K_inD</td>
<td>turnover number of HCO(_3)_ dehydration reaction via CA</td>
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<tr>
<td>K_H</td>
<td>Michaelis constant of CO(_2) hydration via CA</td>
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<tr>
<td>K_D</td>
<td>Michaelis constant of HCO(_3)_ dehydration reaction via CA</td>
</tr>
<tr>
<td>( [Na^+] )</td>
<td>[Na(^+)] in blood plasma</td>
</tr>
<tr>
<td>( [Na^+] )</td>
<td>[Na(^+)] in plasma</td>
</tr>
<tr>
<td>Prefix 'i': Ionic concentrations independent of [HCO(_3)_](^+) and [HCO(_3)_](^-)</td>
<td></td>
</tr>
<tr>
<td>RQ_avCO _2</td>
<td>( \text{av}[CO_2]/\text{av}[O_2] ): respiratory quotient at steady state in vivo</td>
</tr>
<tr>
<td>SID</td>
<td>strong ion difference ([Na(^+)] + [K(^+)] - [C(^-)])</td>
</tr>
<tr>
<td>Y</td>
<td>ratio of [CO(_3)_] in vivo to the CO(_2) content difference between oxygenated and deoxygenated blood measured in vivo (2.65 mmol)</td>
</tr>
</tbody>
</table>
occur simultaneously. In addition, the osmotic pressure or [SID] in the interstitial fluid will become greatly different from that in plasma at steady state. Thus, the relationship between [HCO$_3^-$] and P$_{CO_2}$ at steady state will not be observed in arterial blood in acute hypercapnia.

Table 4 shows that the ionic concentrations in plasma are all given by linear combinations of [HCO$_3^-$]* and [HCO$_3^-$]o. [HCO$_3^-$]* is the sum of [HCO$_3^-$]P (Eq. 7) and [HCO$_3^-$]HE (Eq. 19), and [HCO$_3^-$]o corresponds to the metabolic component of [HCO$_3^-$]. Thus, the equation for [HCO$_3^-$]* (Eq. 4) will be greatly appreciated as a criterion for analysing the acid-base status at steady state in vivo.

The symbols and notations used for main parameters are tabulated in Table 5 to promote understanding.

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