Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise

XING-GUO SUN, JAMES E. HANSEN, WILLIAM W. STRINGER, HUA TING, AND KARLMAN WASSERMAN

Division of Respiratory and Critical Care Physiology and Medicine, Harbor-University of California Los Angeles Medical Center, Torrance, California 90509–2910

Received 23 May 2000; accepted in final form 12 December 2000

Sun, Xing-Guo, James E. Hansen, William W. Stringer, Hua Ting, and Karlman Wasserman. Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. J Appl Physiol 90: 1798–1810, 2001.—To calculate cardiac output by the indirect Fick principle, CO2 concentrations (CCO2) of mixed venous (CvCO2) and arterial blood are commonly estimated from PCO2, based on the assumption that the CO2 pressure-concentration relationship (P CO2-CCO2) is influenced more by changes in PCO2 than by changes in pH. The purpose of the study was to measure and assess the relative importance of these variables, both in arterial and mixed venous blood, during rest and increasing levels of exercise to maximum (Max) in five healthy men. Although the mean mixed venous PCO2 rose from 47 Torr at rest to 59 Torr at the lactic acidosis threshold (LAT) and further to 75 Torr at Max, the CvCO2 rose from 22.8 mM at rest to 25.5 mM at LAT but then fell to 23.9 mM at Max. Meanwhile, the mixed venous pH fell from 7.36 at rest to 7.30 at LAT and to 7.13 at Max. Thus, as work rate increases above the LAT, changes in PCO2 dominate the PCO2-CCO2 relationship, causing CvCO2 to decrease, despite increasing mixed venous PCO2. Furthermore, whereas the increase in the arteriovenous CCO2 difference of 2.2 mM below LAT is mainly due to the increase in CvCO2, the further increase in the arteriovenous CCO2 difference of 4.6 mM above LAT is due to a striking fall in arterial CvCO2 from 21.4 to 15.2 mM. We conclude that changes in buffer base and pH dominate the PCO2-CCO2 relationship during exercise, with changes in Hb and blood oxyhemoglobin saturation exerting much less influence.

lactic acidosis threshold; maximum oxygen consumption; carbon dioxide transport; arteriovenous carbon dioxide difference; cardiac output

OUR LABORATORY RECENTLY demonstrated that direct Fick principle calculated cardiac output using CO2 (CCO2) agrees well with cardiac output calculated from PCO2 (PCO2) and arterial PCO2 (PaCO2) in normal subjects at rest and during exercise (51), as predicted by Fick (16). Other investigators, to avoid blood sampling, have calculated CO2O2 indirectly (7, 12, 15, 29, 36). This approach, although superficially attractive, pays insufficient attention to the effect of pH and change in buffer base on the accuracy and precision of the estimation of CO2 concentration (CCO2) from PCO2, particularly during work rates at which lactate is increased. Blood CCO2 is influenced by pH, PCO2, Hb concentration, and oxyhemoglobin saturation (SO2). During exercise, the CO2 pressure-concentration relationship (P CO2-CCO2) may be more complex than the near-linear relationship depicted in textbooks and the original reports (8, 38, 56), because it is assumed that there is no change in buffer base as CCO2 increases. A frequently referenced report, which presents formulas for refining the influences of PCO2, Hb, and SO2 on CCO2 at rest and during exercise, concludes that “the relationship (P CO2-CCO2) is only slightly influenced by changes in pH” (34). Although some investigators recommend correction for acid-base changes (18, 27), most investigators have calculated the arteriovenous CCO2 difference [mixed venous CCO2 (CvCO2)-arterial CCO2 (CaCO2)] for estimating cardiac output by the indirect Fick method from mixed venous PCO2 (PvCO2) and arterial PCO2 (PaCO2), correcting only for changes in Hb and SO2, but ignoring pH changes (6, 9–11, 26, 31–33, 35, 37, 42).

It is well known that acidaemia due to lactic acidosis occurs with symptom-limiting exercise, both in normal subjects and patients (3, 4, 21, 50–55), resulting in an almost stoichiometric decrease in bicarbonate concentration ([HCO3−]) as lactate increases (46, 48, 55). This intimate relationship challenges the concept that changes in pH only slightly influence CCO2 during exercise. We measured pH, PCO2, Hb, and SO2 in both arterial and mixed venous blood during progressively increasing work rate exercise to maximum (Max) in normal subjects to determine the relative importance of the changes in pH, Hb, and SO2 on the PCO2-CCO2 relationship and on each component in CO2 transport. We hypothesized that, by ignoring changes in acid-base balance during exercise, major errors result in estimates of CCO2 from PCO2 at work rates above the lactic acidosis threshold (LAT). This could translate into ma-

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
METHODS

Subjects, Protocol, and Measures

Subjects. The research protocol was approved by the Human Subjects Committee at Harbor-UCLA Medical Center. Informed consent was obtained from five healthy nonsmoking male subjects that participated in the study.

Catheter placement. A flow-directed pulmonary artery catheter (Arrow International, Reading, PA) was introduced via a femoral vein sheath (Cordis, Miami, FL), which had been inserted percutaneously into the right femoral vein and positioned in the main pulmonary artery under direct fluoroscopic guidance. An arterial catheter was placed percutaneously into the left brachial artery. Each catheter was attached to an infusion apparatus (Contiu-Flo, Baxter Health Care, Deerfield, IL), which provided a slow, continuous flow (15 ml/h) of heparinized normal saline (1,000 U heparin/l) and allowed periodic bolus flushings.

Exercise protocols. An increasing work rate exercise test was performed on an electromagnetically braked cycle ergometer (type 18070, Gould-Godart, Bilthoven, the Netherlands). The rate of work rate increase (range 25–40 W/min) depended on a preliminary, noninvasive increasing work rate exercise test designed to achieve exhaust in ~10 min. Gas-exchange and heart rate measurements were averaged for each 30-s period during 3 min of rest and 3 min of unloaded pedaling and during the progressively increasing work rate test to maximum tolerance. Pedal frequency was maintained at 60 rpm.

Respired-gas analysis. The subjects respired through a mouthpiece during the test. Expired air was directed to a Fleisch type 3 pneumotachograph via a breathing valve (15 ml/h) of heparinized normal saline (1,000 U heparin/l) and allowed periodic bolus flushings.

Exercise protocols. An increasing work rate exercise test was performed on an electromagnetically braked cycle ergometer (type 18070, Gould-Godart, Bilthoven, the Netherlands). The rate of work rate increase (range 25–40 W/min) depended on a preliminary, noninvasive increasing work rate exercise test designed to achieve exhaust in ~10 min. Gas-exchange and heart rate measurements were averaged for each 30-s period during 3 min of rest and 3 min of unloaded pedaling and during the progressively increasing work rate test to maximum tolerance. Pedal frequency was maintained at 60 rpm.

Blood samples. Blood was sampled simultaneously from the pulmonary artery and brachial artery during rest and unloaded cycling and at each minute of increasing work rate exercise. Blood-gas samples were drawn over a 15- to 20-s period. The samples were collected in glass syringes that contained a small amount (mean 0.14 ml) of liquid heparin (1,000 U/ml). The blood samples were agitated to prevent clotting and were immediately placed in an ice slurry.

Blood analyses. Blood-gas analyses were performed by using an Instrumentation Laboratory 1306 blood-gas analyzer (Lexington, MA) for pH, Pco2, and P02 and an Instrumentation Laboratory 482 CO-oximeter for Hb and SO2. The blood-gas analyzer was recalibrated every 20–30 min. Tonometers blood samples were used to verify accuracy. The measured values were corrected for heparin dilution and the known consistent underestimation of blood Pco2 values >45 Torr (23, 51).

Calculation of Cco2, Cvco2-Caco2, CO2CO2, and Plasma [HCO3-]

Values of Cco2, Cvco2-Caco2, CO2CO2, and Plasma [HCO3-]. The plasma CO2 (Cco2 pl) (mM) and plasma [HCO3-] (mM) were calculated from the standard formula derived from the Henderson-Hasselbalch equation (13, 21, 34, 38)

\[
\text{Cco2 pl} = P\text{co2} \times s \times [1 + 10^{\text{pH} - pK'}] \\
\text{Plasma [HCO3-]} = \text{Cco2 pl} - P\text{co2} \times s
\]

where s is the plasma solubility coefficient (in mM/Torr) of CO2 and pK' is the apparent dissociation constant of the CO2-HCO3 system. The variable s is 0.0307 in plasma at 37°C and pH 7.4 in normal human subjects (1). The variable pK' was calculated from Kelman's equation (13, 28), assuming the temperature was stable at 37°C during short-period exercise (51)

\[
pK' = 6.086 + 0.042 \times (7.4 - \text{pH}) + 0.00472 + 0.00139 \times (7.4 - \text{pH})
\]

Total blood Cco2 (mM) was calculated from the equation of Douglas et al. (13), modified from Visser's equation (34) after taking into account the effects of changing pH during exercise on pK'

\[
\text{Cco2} = \text{Cco2 pl} \times 
\frac{0.0289 \times [\text{Hb}]}{(3.352 - 0.456 \times \text{So2}) \times (8.142 - \text{pH})}
\]

where [Hb] is Hb concentration.

After CaCO2 and CvCO2, the CvCO2, Caco2, and concurrent CO2CO2 were calculated, the latter by the Fick principle (16).

Default values of Caco2, CvCO2-Caco2, and CO2CO2. To compare the magnitude of error caused by the failure to acknowledge changes in pH, Hb, and SO2 from rest to exercise on the Pco2-Caco2 relationship, default (Def) values of Caco2 were calculated by using the resting values of pH, Hb, and/or SO2 for each individual. Def values are so named because they do not acknowledge the changes in one or more of the independent variables during exercise. For example, if the changing Pco2, Hb, and SO2 values were used to calculate Caco2 during each minute of exercise but the pH remained at its resting (or actual) value, the Caco2 would be identified as Def-pH Caco2. In this way, we calculated Def-Hb, Def-SO2, and the combined Def-pH, Hb and SO2, the latter when changes in all three values were not taken in to account. The percent errors of the Def values from the actual values of Caco2, CvCO2, Cvco2-Caco2, and CO2CO2 for each stage of exercise were calculated using the following formula: %error = 100 \times (\text{actual} - \text{actual}) / \text{actual}.

Relative importance of multiple factors on the Pco2-Caco2 relationship during exercise. Besides physically dissolved CO2 ([CO2]), which depends only on Pco2 under isometric conditions, the two major factors influencing the Pco2-Caco2 relationship in the Douglas equation are the HCO3 factor (Fbic, i.e., the effect of pH on the quantity of [HCO3-] in both plasma and red blood cell) and the Hb factor (Fh, i.e., the effect of Hb binding to CO2). The Fbic consists of three
subfactors, the Hb concentration ($F_{HbpH}$), the SO$_2$ ($F_{HbSO_2}$), and the pH ($F_{HbPH}$) on Hb binding of CO$_2$. The formulas for the two major factors and the three subfactors are given in APPENDIX A. After calculation of actual values of each factor and subfactor using these equations, the relative importance of the changes in each factor and subfactor at each stage of exercise was calculated. Thus the influence of a specific factor or subfactor at any stage of exercise depends on how far its ratio differs from 1.00.

**Estimation of Each Component of Blood CO$_2$ During Exercise**

The CO$_2$ is transported as six components in human blood, [CO$_2$], [HCO$_3$], and carbamino concentration ([NH-CO$_2$]) in both the plasma and the red blood cell. To compare the relative importance and change of each component of CO$_2$ during exercise, we calculated each of these six components using the equations in APPENDIX B.

**Data Analysis and Statistics**

Unless otherwise specified, all data are expressed as means ± SD, with range values in parentheses. Data were analyzed predominantly by ANOVA; paired t-tests were used only when specified. The values of CO$_2$ calculated from Douglas’ equation and APPENDIX B were compared by using linear regression and Pearson product-moment correlation coefficients. A $P < 0.05$ was considered significant.

**RESULTS**

The subject’s physical characteristics and aerobic parameters were as follows: age, 25 ± 5 (20–34) yr; height, 179 ± 3 (173–183) cm; body weight, 73 ± 5 (68–80) kg; work rate at LAT, 126 ± 25 (98–154) W; maximum work rate, 302 ± 47 (225–360) W; $V_{O_2}$ at LAT, 2.00 ± 0.31 (1.50–2.35) l/min; and maximal $V_{O_2}$, 3.91 ± 0.61 (2.74–4.31) l/min. From rest to Max, $V_{O_2}$ increased over 10-fold, from 0.37 ± 0.04 to 3.91 ± 0.61 l/min; $V_{CO_2}$ increased over 16-fold, from 0.29 ± 0.04 to 4.84 ± 0.71 l/min; heart rate increased nearly threefold, from 63 ± 6 to 178 ± 12 beats/min; whereas cardiac output increased over threefold, from 7.06 ± 2.37 to 25.38 ± 3.90 l/min. The rate of increase in $V_{O_2}$ as related to work rate increase was 10.03 ± 0.61 l/min; $V_{O_2}$ increased over 10-fold, from 0.37 to 3.91 l/min; CO$_2$ increases were marked, similar to that previously reported (24, 25, 52).

**Actual Changes in Blood CO$_2$ Content**

Both mixed venous and arterial Hb increased slightly but significantly above the LAT as Max was approached ($P < 0.05$ to $P < 0.01$) (Table 1). Mixed venous values for Hb are not shown because they differed minimally from arterial values (0.2 ± 0.3 g/dl). The mixed venous SO$_2$ progressively decreased from rest to Max ($P < 0.05$ to $P < 0.001$), whereas arterial SO$_2$ decreased slightly near Max ($P < 0.05$) (Table 1). Both mixed venous pH ($pH_v$) ($P < 0.05$ to $P < 0.001$) and arterial pH ($pH_a$) ($P < 0.05$) progressively decreased from rest to Max, with $pH_a$ decreasing more than the $pH_v$ ($P < 0.05$ to $P < 0.01$ by paired t-test) (Fig. 1 and Table 1). $P_{CO_2}$ increases were marked, with progressively increasing values from rest to Max, particularly above the LAT ($P < 0.05$ to $P < 0.001$).
PaCO2 increased slightly from rest (P < 0.05) to LAT, then stabilized, and then decreased moderately near Max (P < 0.01 vs. LAT; P < 0.05 vs. rest value) (Fig. 1). Thus mixed venous-arterial differences of O2 concentration, CvO2-CaO2 (Fig. 1), SO2, pH, and PO2 all progressively increased from rest to Max (P < 0.05 to P < 0.001) (Table 1).

It is impressive how little change took place in CvCO2 from rest (23 mM) to Max (24 mM), despite large changes in Pco2 (47–78 Torr) (see Figs. 1 and 2 and Table 2). Initially, as exercise became more intense, CvCO2 increased more than CaCO2. CvCO2 then stabilized, whereas CaCO2 began to decrease (P < 0.05 or P < 0.01) (Fig. 1). As exercise increased to maximum, the CvCO2 decreased from its peak level (Table 2, at 5 min of incremental exercise) to slightly above its rest value in the case of CvCO2 (P < 0.01) and below the rest value in the case of mixed venous [HCO3-] (Fig. 2B).

In contrast, CaCO2 decreased to a much greater degree with little change in Paco2. Thus the progressive increase in CvCO2-CaCO2 below LAT was due to an increasing CvCO2, whereas above LAT it was primarily due to a decreasing CaCO2 (Fig. 2).

Errors in Def CO2 and CO2O2 During Exercise

Table 2 shows the absolute values and percent errors of Def-pH CO2O2 from actual CO2O2 values. Errors in CvCO2, CaCO2, and CvCO2-CaCO2 increased consistently from actual values as exercise intensity increased, because changes in pH were not accounted for during exercise (P < 0.05 below LAT; P < 0.01 above LAT). Although errors in CvCO2 and CaCO2 were directionally the same, the absolute and percent errors of Def-pH CvCO2 were always larger than those of Def-pH CaCO2 (P < 0.001 by paired t-test), resulting in consistent overestimation of Def-pH CvCO2-CaCO2. Although abso-
lute errors of Def-pH CaCO2-CaCO2 were always smaller than either those of Def-pH CVCO2 or Def-pH CaCO2 (Table 2; $P < 0.001$ by paired t-test). The overestimation of CaCO2, CVCO2, and CVCO2-CaCO2 that results from failure to use pH in the calculation of CCO2 ranged from $-0.2$ to $27, 2$ to $60$, and $18$ to $120\%$, respectively, even when correct, directly measured arterial and mixed venous PCO2, Hb, and SO2 are used in the calculation.

Figure 3 shows the percent errors of specific Def values of CVCO2-CaCO2, despite the use of correct measurements of PCO2, when no change during exercise is assumed in Hb, SO2, and/or pH. Defaulting changes in Hb during exercise results in trivial error (only $-0.2$ to $0.6\%$). Defaulting the change in SO2 results in slight underestimation in CVCO2-CaCO2 over the entire exercise period ($-6$ to $-3\%$; $P < 0.05$). In contrast, defaulting changes in either pH alone or pH, Hb, and SO2 together cause large errors, i.e., a progressive overestimation in CVCO2-CaCO2 as exercise intensity increases, reaching $-50\%$ at LAT and $100\%$ at Max.

As seen in Fig. 4, the percent errors in COCO2 that result from defaulting the influence of Hb, SO2, and/or pH on the PCO2-CCO2 relationship are always opposite to those on CVCO2-CaCO2. As with its effect on CVCO2-CaCO2, the change in Hb causes a trivial effect on COCO2 (only $-0.6$ to $0.2\%$), whereas the changes in SO2 cause the estimate of COCO2 to be $3$–$6\%$ higher than actual ($P < 0.05$). In contrast, defaulting changes in either pH alone or pH, Hb, and SO2 together causes errors in COCO2 by $>30\%$ at LAT and $>50\%$ at Max.

Relative importance of multiple factors on the PCO2-CCO2 relationship during exercise. The influence of each of several factors on the PCO2-CCO2 relationship is shown in Table 3, with factor influence increasing as its value deviates from 1.0. Thus the deviations during exercise of Fbic (which are due to pH changes) far exceed those of FHb, both in mixed venous and arterial blood, during exercise (Table 3). Considering the subfactors of FHb, the deviations during exercise of FHBa (due to the effect of pH changes on [NH-CO2]) exceed those of FHBao, and FHBaa, both in mixed venous and arterial blood. Thus the changes and influence of pH (Fbic and FHBa) are quantitatively much more important in blood CO2 transport during exercise, both in mixed venous and arterial blood, than are the changes and influences of change in Hb and SO2. These findings contrast importantly with the conclusions of McHardy (34).

Changes in Blood Components of CO2 During Exercise

The total CO2 and each of its fractional components in mixed venous and arterial blood and the mixed venoarterial differences at rest and during exercise are shown in Fig. 5 and Table 4. These data were calculated from the equations described in APPENDIX B. Both CVCO2 and CaCO2 correlated well with the same variables calculated from the Douglas equation ($r = 0.9998, P < 0.0001$), with only very small deviations ($-0.06 \pm 0.14$ mM) at rest and during exercise.
In Fig. 5, both mixed venous [CO₂] and [NH-CO₂] increased progressively from rest to Max (P < 0.05). Smaller percent but larger absolute changes in [HCO₃⁻] dwarfed the impact of the larger percent but smaller absolute changes in mixed venous [CO₂] and [NH-CO₂]. Below LAT, trends in change in CvCO₂ were similar to those in [CO₂] or [NH-CO₂], but they differed markedly above LAT. The arterial [CO₂] and [NH-CO₂] increased only slightly from rest at LAT (P < 0.05) and then returned to near resting values at the highest work rate. In contrast to the relatively stable arterial [CO₂] and [NH-CO₂], large declines in arterial [HCO₃⁻] above the LAT caused marked decreases in CaCO₂.

![Image](http://jap.physiology.org/)

Fig. 3. Errors in CvCO₂-Caco₂ during exercise caused by ignoring changes in pH, Hb, and/or SO₂ from resting values. Horizontal dotted line, actual value at each point calculated from measured mixed venous and arterial PCO₂, pH, Hb, and SO₂ at rest and during exercise, normalized to 0. Values are means ± SE. Each symbol indicates percent errors of CvCO₂-Caco₂ from the actual values caused by ignoring exercise-induced changes from rest in pH, Hb, and/or SO₂ in mixed venous and arterial blood, despite correct values for FvCO₂ and PaCO₂. Ignoring changes in pH or all 3 variables from rest causes overestimation of CvCO₂-Caco₂ by 3–6%. Ignoring changes in SO₂ from rest causes underestimation of CvCO₂-Caco₂ by 3–6%. Ignoring changes in values of Hb causes trivial underestimation of CvCO₂-Caco₂. Vo₂/Vo₂@LAT, ratio of Vo₂ to Vo₂@LAT.

Fig. 4. Errors in cardiac output using CO₂ (COCO₂) during exercise caused by ignoring changes in pH, Hb, and/or SO₂ from resting values. Horizontal dotted line, actual value at each point calculated from measured mixed venous and arterial PCO₂, pH, Hb, and SO₂ at rest and during exercise and CO₂ production, normalized to 0. Values are means ± SE. Each symbol indicates percent errors of COCO₂ from the actual values caused by ignoring exercise-induced changes in pH, Hb, and/or SO₂ in mixed venous and arterial blood, despite correct values for FvCO₂ and PaCO₂. Ignoring changes in pH or all 3 variables from rest causes underestimation of COCO₂ by 10.2% on October 15, 2017. **Table 2. Comparison of actual and default pH values on blood CO₂ concentration during exercise**

<table>
<thead>
<tr>
<th>Exercise Level</th>
<th>Actual Values</th>
<th>Def-pH Values</th>
<th>%Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CvCO₂, mM</td>
<td>Caco₂, mM</td>
<td>CvCO₂-Caco₂, mM</td>
</tr>
<tr>
<td>Rest</td>
<td>22.79 ± 1.41</td>
<td>20.87 ± 1.16</td>
<td>1.92 ± 0.39</td>
</tr>
<tr>
<td>Unl</td>
<td>23.37 ± 1.20</td>
<td>21.35 ± 0.89</td>
<td>2.07 ± 0.55</td>
</tr>
<tr>
<td>Ex-1</td>
<td>24.03 ± 1.53a</td>
<td>21.13 ± 1.18</td>
<td>2.90 ± 0.54b</td>
</tr>
<tr>
<td>Ex-2</td>
<td>24.38 ± 1.53a</td>
<td>21.47 ± 1.26</td>
<td>2.91 ± 0.67a</td>
</tr>
<tr>
<td>Ex-3</td>
<td>24.60 ± 1.28b</td>
<td>21.60 ± 1.32</td>
<td>3.00 ± 0.60c</td>
</tr>
<tr>
<td>Ex-4</td>
<td>25.46 ± 1.56b</td>
<td>21.41 ± 1.52</td>
<td>4.05 ± 0.76e</td>
</tr>
<tr>
<td>Ex-5</td>
<td>25.82 ± 1.52a</td>
<td>21.13 ± 1.39</td>
<td>4.79 ± 0.42h</td>
</tr>
<tr>
<td>Ex-6</td>
<td>25.78 ± 1.35b</td>
<td>20.73 ± 1.62</td>
<td>5.05 ± 0.42i</td>
</tr>
<tr>
<td>Ex-7</td>
<td>25.54 ± 1.68b</td>
<td>19.56 ± 1.85</td>
<td>5.98 ± 0.93j</td>
</tr>
<tr>
<td>Ex-8</td>
<td>25.14 ± 1.77b</td>
<td>18.38 ± 2.14</td>
<td>6.72 ± 0.88k</td>
</tr>
<tr>
<td>Max</td>
<td>23.88 ± 2.55</td>
<td>15.25 ± 2.62b</td>
<td>8.63 ± 1.01l</td>
</tr>
</tbody>
</table>

Values are means ± SD. Default pH (Def-pH) values for blood CO₂ concentrations in mixed venous (CvCO₂), arterial (Caco₂), and their difference (CvCO₂-Caco₂) were calculated by ignoring changes from resting values for pH with Douglas’ equation (13). %Error = (actual - default) / actual × 100. Significantly different from rest: *P < 0.05, †P < 0.01, ‡P < 0.001. Significant difference, Def-pH vs. actual values by paired t-test: 4P < 0.05, 5P < 0.01, 6P < 0.001.
Table 3. Factors describing the magnitude by which Hb, SO2, or pH changes affect the Pco2-CCO2 relationship during exercise

<table>
<thead>
<tr>
<th>Exercise Level</th>
<th>Mixed Venous Blood</th>
<th>Arterial Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fbic</td>
<td>Fhbl</td>
</tr>
<tr>
<td>Rest</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Unl</td>
<td>0.98±0.02*</td>
<td>1.01±0.00</td>
</tr>
<tr>
<td>Ex-1</td>
<td>0.97±0.02*</td>
<td>1.01±0.00*</td>
</tr>
<tr>
<td>Ex-2</td>
<td>0.95±0.01*</td>
<td>1.01±0.00*</td>
</tr>
<tr>
<td>Ex-3</td>
<td>0.92±0.02</td>
<td>1.01±0.01*</td>
</tr>
<tr>
<td>LAT</td>
<td>0.87±0.03</td>
<td>1.02±0.01*</td>
</tr>
<tr>
<td>Ex-5</td>
<td>0.84±0.03</td>
<td>1.03±0.01*</td>
</tr>
<tr>
<td>Ex-6</td>
<td>0.80±0.04</td>
<td>1.03±0.01*</td>
</tr>
<tr>
<td>Ex-7</td>
<td>0.75±0.04</td>
<td>1.04±0.01*</td>
</tr>
<tr>
<td>Max</td>
<td>0.70±0.06</td>
<td>1.04±0.01*</td>
</tr>
</tbody>
</table>

Values are means ± SD. CO2, CO2 concentration; Fbic, pH factor of plasma and red cell bicarbonate; Fhbl, Hb CO2 binding factor; FHbHb, Hb subfactor of Hb CO2 binding; FCO2SO2, SO2 subfactor of Hb CO2 binding; Fbic, pH subfactor of Hb CO2 binding. Factors describe the relative values of variables in the Douglas equation (see Eq 5 and APPENDIX A). In our subjects, resting factors values are Fbic = 18.69 ± 0.54, Fhbl = 0.81 ± 0.01, Fbic = 0.45 ± 0.01, Fbic = 0.33 ± 0.003, and Fbic = 1.28 ± 0.02 in mixed-venous blood and for arterial blood are Fbic = 20.06 ± 0.48, Fbic = 0.79 ± 0.01, Fbic = 0.45 ± 0.01, Fbic = 0.34 ± 0.000, and Fbic = 1.34 ± 0.02. Values show the relative changes in factors from their resting values. The further the values differ from 1.00, the greater their influence on the Pco2-CCO2 relationship. Significant difference vs. rest: *P < 0.05, †P < 0.01, ‡P < 0.001.

Thus changes in CvCO2 and Caco2, respectively, are dwarfed by the changes in [HCO3-] with changes in [CO2] and [NH-CO2] having a relatively small effect.

Referring to Table 4 (selected exercise intensities), ratios of CO2 to [CO2] (CCO2/[CO2]) were calculated by dividing the CCO2 by the sum of plasma and red blood cell components of [CO2]. Note that the CCO2/[CO2] for mixed venous blood progressively decreased as the exercise intensity increased (P < 0.05), especially above LAT (P < 0.01). The CCO2/[CO2] in arterial blood, which did not change significantly below LAT (P > 0.05), progressively decreased at and above LAT (P < 0.05), because of the reduction in [HCO3-]. Thus CCO2/[CO2] is not constant but depends on the source of blood and the intensity of exercise.

It is also evident from Table 4 and Fig. 5 that plasma and red blood cell [HCO3-] together comprise ~85% (mixed venous) and 90% (arterial) of the CCO2 at rest and during exercise. Even though the absolute values of mixed venous [HCO3-] are always greater than those of the arterial [HCO3-], the mixed venous [HCO3-]/CCO2 are always lower than the arterial [HCO3-]/CCO2 (P < 0.001) because of the greater amount of [CO2].

Relative contributions of the three forms of CO2-to-CO2 exchange are shown for each level of exercise in Table 5. From rest to Max, [HCO3-] exchange remained large and quite constant at ~76–77% of total CO2 excreted, i.e., CvCO2-Caco2. In contrast, [CO2] and [NH-CO2] accounted for ~9 and 14%, respectively, of total CO2 excreted at rest. Above LAT, the relative contribution to CO2 output of [CO2] progressively increased to 13% (P < 0.05) and that of [NH-CO2] decreased to ~10% (P < 0.01).

Finally, to support the validity of our calculated values for Caco2, CvCO2, and Caco2-Caco2 at all levels of exercise, we compared the CCO2 measured by the Fick principle with CO2 at rest and each level of exercise for the five subjects in this study (Table 6). At each level but Max, the mean values are in good agreement. As noted in Table 6, in other quite similar exercise studies (51), the CO2 was insignificantly different from CO2 at peak and all other levels of exercise.
DISCUSSION

Major Findings

This study discloses several important findings. 1) During exercise, CO₂ and [HCO₃⁻] do not consistently increase in proportion to P CO₂. 2) Because of the acidemia caused by increased lactate production, CCO₂₃ and mixed venous [HCO₃⁻] decrease to near resting values as maximal VO₂ is approached, despite increasing P VCO₂. 3) Above LAT, while P VCO₂ increases to high levels, PaCO₂ decreases because of ventilatory compensation for the exercise lactic acidosis; consequently, CacO₂ decreases to a greater degree than does C VCO₂. 4) The increase in C VCO₂-Caco₂ during exercise is mainly due to the increase in C VCO₂ below LAT and the decrease in CacO₂ above LAT. 5) Changes in SO₂ and Hb have minor influences on the P CO₂-Caco₂ relationship during exercise, whereas changes in pH due to changes in buffer base have a major influence. 6) Because pHv decreases more than pHa, there are large errors in calculated C VCO₂-Caco₂ when the pH change is ignored. 7) At rest and during all levels of exercise, over three-fourths of the total CO₂ exchange from the blood to lung gas (i.e., CV CO₂-Caco₂) is due to dissociation of [HCO₃⁻], whereas less than one-fourth is due to the combination of venoarterial differences in [CO₂] and [NH-CO₂] at rest to Max.

The Dominant Role of pH in the P CO₂-Caco₂ Relationship During Exercise

As evidenced by V CO₂ measurements during exercise, the lung progressively increases the excretion of CO₂ as work rate increases. Because cardiac output increases much less than V CO₂, the difference between C VCO₂ and Caco₂ necessarily widens. Figures 1 and 2 depict the progressive increase in the differences among C VCO₂, Caco₂, [HCO₃⁻], P CO₂, and pH as work increases.

Table 6. Comparison of cardiac output by Fick method using CO₂ or O₂ at rest and different levels of exercise

<table>
<thead>
<tr>
<th>Stage</th>
<th>CO₂ CO₂/min</th>
<th>CO₂ CO₂/min</th>
<th>Ratio CO₂ CO₂/min</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>6.66 ± 1.79</td>
<td>6.65 ± 2.03</td>
<td>1.01 ± 0.03</td>
<td>0.93</td>
</tr>
<tr>
<td>Unl</td>
<td>9.31 ± 1.67</td>
<td>9.44 ± 1.59</td>
<td>0.99 ± 0.04</td>
<td>0.59</td>
</tr>
<tr>
<td>Ex-1</td>
<td>11.61 ± 2.08</td>
<td>12.19 ± 2.39</td>
<td>0.96 ± 0.04</td>
<td>0.25</td>
</tr>
<tr>
<td>Ex-2</td>
<td>13.20 ± 3.77</td>
<td>13.33 ± 3.51</td>
<td>0.99 ± 0.08</td>
<td>0.84</td>
</tr>
<tr>
<td>Ex-3</td>
<td>15.43 ± 3.93</td>
<td>15.36 ± 3.94</td>
<td>1.02 ± 0.09</td>
<td>0.50</td>
</tr>
<tr>
<td>LAT</td>
<td>17.52 ± 3.66</td>
<td>17.37 ± 3.61</td>
<td>1.00 ± 0.07</td>
<td>0.89</td>
</tr>
<tr>
<td>Ex-5</td>
<td>18.31 ± 3.12</td>
<td>18.16 ± 3.25</td>
<td>1.01 ± 0.05</td>
<td>0.73</td>
</tr>
<tr>
<td>Ex-6</td>
<td>20.63 ± 3.92</td>
<td>20.33 ± 3.43</td>
<td>1.01 ± 0.05</td>
<td>0.61</td>
</tr>
<tr>
<td>Ex-7</td>
<td>21.59 ± 4.76</td>
<td>21.13 ± 3.97</td>
<td>1.01 ± 0.05</td>
<td>0.43</td>
</tr>
<tr>
<td>Ex-8</td>
<td>22.52 ± 5.32</td>
<td>22.09 ± 4.32</td>
<td>1.02 ± 0.06</td>
<td>0.43</td>
</tr>
<tr>
<td>Max</td>
<td>23.86 ± 6.34</td>
<td>22.66 ± 5.36</td>
<td>1.05 ± 0.04†</td>
<td>0.05</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1.01 ± 0.06†</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Values are means ± SD. CO₂ CO₂ CO₂ CO₂ cardiac output using CO₂, CO₂ CO₂ cardiac output using O₂. *CO₂ CO₂ compared with CO₂ using paired t-test. †When compared with a larger number of similar studies, mean value of CO₂ CO₂ ratio at maximal exercise is 1.02 (P = 0.29, n = 10), whereas the mean CO₂ CO₂ ratio of all 112 measurements is 1.00.
rate increases. The metabolic acidosis found in our subjects during high-intensity exercise causes plasma and red blood cell CCO2 and [HCO3] to decrease in both mixed venous and arterial blood, but especially in arterial blood.

As commonly graphed, the PCO2-CCO2 relationship is depicted as nearly linear between PCO2 values of \(-30–80 \text{Torr}\) and CCO2 values of \(-12–28 \text{mM}\) but without reference to or depiction of the effect of a pH change (8, 38, 56). Changes in CCO2 are sometimes fractionated into plasma and red blood cell components, and the differences between mixed venous and arterial blood due to Hb and SO2 are also considered, again with exclusion of the effect of pH (8, 38, 56). However, as seen in Figs. 1 and 2A and Tables 1 and 2, widely divergent P\text{VCO2} values (47–78 Torr) may occur with reasonably similar C\text{VCO2} values (22.8–23.9 mM). This is due to relatively large decreases in the buffer base reflected in the change in pH \(7.362–7.130\) (Table 1 and Fig. 1). Furthermore, reasonably similar P\text{ACO2} values (41–38 Torr) may pair with widely different C\text{ACO2} values (20.9–15.2 mM) because of relatively large differences in pH. Thus when the C\text{VCO2} is calculated from P\text{VCO2}, the change in blood pH during exercise must not be ignored. During heavy exercise, CCO2 is not linearly related to the PCO2 in either arterial or mixed venous blood (see Fig. 2A). In fact, PCO2 and CCO2 change in opposite directions in mixed venous blood as metabolic acid is added to the blood by the muscles. In contrast to original reports and textbooks (8, 38, 56), Fig. 2 shows that C\text{VCO2} does not increase as a function of P\text{VCO2} during exercise above the LAT.

We suggest that the addition of pH (or [H\(^+\)]) isopleths to diagrams depicting the plasma [HCO\(_3\)]-PCO2 and CCO2-PCO2 relationships, such as shown in Fig. 2, conveys necessary and important information that is lacking in the present standard depictions of these relationships (8, 38, 56). Such isopleths clarify and reinforce the importance of the acid-base changes that can occur during exercise.

Total blood [HCO\(_3\)] comprises \(-85\%\) (mixed venous) or 90\% (arterial) of the CCO2 (Table 4). Although the percent changes in mixed venous [CO2] and [NH\(_2\)-CO2] are appreciable (Tables 4 and 5 and Fig. 5), their impact is dwarfed by the magnitude of the large absolute changes in [HCO\(_3\)]. Additionally, Tables 2 and 3 and Fig. 3, which give Def values and factor ratios, analyze the relative importance of the components of CCO2 in the Douglas equation and confirm the dominance of pH factors. In Table 3 and Fig. 3, it is shown that the pH change factor (F\text{bic} from 1.00 at rest to 0.59 at Max) dominates over other factors. Within the red blood cell, the pH factor even dominates over the change in Hb concentration and SO2 factors (Table 3). Thus making adjustments for the influences of Hb and SO2 while ignoring pH to calculate C\text{VCO2} or C\text{ACO2} during exercise, as was done earlier (34), results in major errors.

Relevance of the CCO2-PCO2 Relationship to the Accuracy and Precision of Estimation of C\text{VCO2}-C\text{ACO2} and C\text{CO2}

Our calculations of CCO2 come from direct measurements of mixed venous and arterial PCO2, pH, Hb, and SO2. As previously shown, the relationship between PCO2 and CCO2 is positively correlated between rest and LAT but then becomes negatively correlated as increasing metabolic acidosis develops. Thus a given PCO2 value can be associated with widely divergent CCO2 values.

It would be convenient if errors in measurement of C\text{VCO2} and C\text{ACO2} were to be offset in the calculation of C\text{VCO2}-C\text{ACO2}, but this is not the case. It is evident from Table 2 that omitting the change in pH in calculating C\text{VCO2}-C\text{ACO2} causes a much larger error than when C\text{VCO2} and C\text{ACO2} are calculated individually. Figure 4 shows that, when these erroneous measurements are applied to calculate cardiac output, errors of large magnitude result. In contrast, ignoring the changes in [Hb] and SO2 during exercise results in relatively unimportant errors compared with ignoring changes in pH.

Possible Measurement and Calculation Errors in Our Data

The gas exchange, rate of increase in VO2 as related to work rate increase, and mixed venous and arterial blood values are unlikely to be significantly inaccurate or imprecise in this study, considering the similarity of these values to those of other studies in normal men and the quality control procedures used in our laboratory (3, 4, 21, 24, 25, 46–55). A limitation of this study is the absence of direct measurements of C\text{ACO2} and C\text{VCO2}. Because all methods for such measurements require a minimum of 30 min for each blood sample, it was unrealistic to obtain the many measurements needed on so many samples (~24–28) for each study. However, the similar values obtained for CO2 and C\text{CO2} at rest and all levels of exercise (Table 6) give credence to the reliability of the concurrent measurements of pH and PCO2 and calculated mixed venous and arterial concentrations of CO2 and O2 at all levels of exercise.

We did not measure blood or body temperatures during exercise. From other studies using a similar exercise protocol, we estimated that the temperature increase from rest to peak exercise would be 0.2–0.8°C (51). We calculated that a temperature rise of 0.5°C during exercise would affect the values of C\text{ACO2}, \text{C\text{VCO2}}, and C\text{VCO2}-C\text{ACO2} by <1% at peak exercise (51). Therefore, this small temperature change would not significantly alter our findings.

Considering the diversity of sources and complexity of equations in APPENDIX B that were used to calculate the six components of CCO2, the sum values for each blood sample from the six sources agree remarkably well with those calculated from the simpler Douglas equation. The CCO2 values calculated from the Douglas equation have excellent linear correlation with the
Possible Errors Due to a Disequilibria of pH and CO₂

There is no evidence that an alveolar-arterial CO₂ disequilibrium occurs, except under conditions of high levels of carbonic anhydrase inhibition. The latter is a model of CO₂ disequilibrium. In contrast, there are good arguments using physiological data against disequilibrium for CO₂ at high work rates as follows.

1) End-tidal PCO₂ (PETCO₂) exceeds Paco₂ during exercise with a maintained negative Paco₂-PETCO₂ difference of ~4 Torr, despite the increase in VCO₂ to very high levels (54). If there were a disequilibrium, Paco₂-PETCO₂ difference and Paco₂ should increase relative to PETCO₂ as VCO₂ increases. However, the change in PETCO₂ parallels the change in Paco₂, as VCO₂ increases to maximum and remains above it (54).

2) If there were a disequilibrium, calculated dead space volume/tidal volume should increase as work rate increases, because Paco₂ would be increased relative to PETCO₂. This happens when a right-to-left shunt opens during exercise but does not happen normally. Dead space volume/tidal volume decreases with exercise and remains decreased to similar levels or decreases further as work rate increases to the maximum in normal subjects.

3) If there were a disequilibrium, V̇CO₂ would not increase appropriately as high-metabolic rates are achieved and Paco₂ would increase. Increasing V̇CO₂ keeps pace with increasing VO₂ even for very fit men and exceeds VO₂ once lactic acidosis occurs. If metabolic CO₂ plus CO₂ released from buffer were retained because of an alveolar-capillary disequilibrium as blood passed from pulmonary artery to pulmonary vein, we might expect to see a higher Paco₂ and arterial [HCO₃⁻]. In fact, Paco₂ and arterial [HCO₃⁻] decrease, without any evidence of CO₂ retention.

4) The decrease in arterial [HCO₃⁻] is approximately equal to the increase in arterial lactate during high levels of exercise. If there were a disequilibrium, [HCO₃⁻] would be relatively high, because it would not dissociate adequately in its passage from pulmonary artery to systemic artery. In fact, despite the very high ṖVCO₂ for work above the LAT (Fig. 1), the Paco₂ and [HCO₃⁻] decrease more than that of the mixed venous blood. Our major finding is that the decrease in Caco₂ is the primary explanation for the increase in ĊVCO₂-ĊCaCO₂ during exercise at high work rates above the LAT, not the increase in ĊVCO₂. This contradicts the changes we would see if there were a disequilibrium of significance.

Relative Contributions of Components of Blood CO₂-to-CO₂ Exchange Across the Lung

Table 5 illustrates that the contribution of [HCO₃⁻] to CO₂ exchange is relatively constant as a percentage of ĊVCO₂-ĊCaCO₂. In contrast, the contribution of [CO₂] increases and [NH-CO₂] decreases as exercise intensity increases. This is because [CO₂] is influenced only by Pco₂, whereas [NH-CO₂] is also influenced by SO₂ and pH.

The traditional dissociation curve for CO₂ over the range of 30 to 70–80 Torr depicted in textbooks (8, 38, 56) suggests that a large part of the ĊVCO₂-ĊCaCO₂ is dependent on the SO₂ difference between mixed venous and arterial blood. Considering the relative contributions of all components to CO₂ exchange that account for the increase in ĊVCO₂-ĊCaCO₂ during exercise, our study shows that [HCO₃⁻] accounts for over three-fourths of the total difference at rest and at all levels of exercise, whereas [CO₂] and [NH-CO₂], in combination, account for less than one-fourth of the total difference. Of this, approximately three-fifths come from [NH-CO₂] and two-fifths come from [CO₂] below LAT. This relationship reverses as work rate increases above LAT.

The difference in ĊCO₂ caused by changing the state of oxygenation of the blood at the same Pco₂ is fully attributable to the change in red blood cell [NH-CO₂]. Our calculations of [NH-CO₂] in ĊVCO₂ and in ĊCaCO₂ at rest are not in agreement with earlier reports (38, 44), which estimated that one-third of CO₂ exchange was attributable to oxygen-induced changes in [NH-CO₂]. These earlier studies used blood devoid of 2,3-diphospho-D-glycerate (DPG). Later studies in blood that considered the effect of DPG (2, 30) found that the [NH-CO₂] contribution to CO₂ exchange at rest is only between 10 and 15%, in close agreement with our finding of 14%. If we had ignored the DPG effect, our ĊCO₂ values calculated from APPENDIX B would have deviated further from the Douglas equation ĊCO₂ values.

It is clear that the dissociation of [HCO₃⁻] plays the dominant role in CO₂ exchange at the lung, whereas [CO₂] and [NH-CO₂] play smaller roles in total CO₂ exchange. Although Pco₂ differences account for the transfer of CO₂ out of blood, >75% of the quantity transferred comes from the dissociation of mixed venous [HCO₃⁻]. We have shown that ĊVCO₂ in blood actually decreases during exercise above the LAT, despite increasing Pco₂. The major reason for this is that the CO₂ dissociation curve is shifted downward when lactic acid is generated during exercise. Simultaneously, the ṖVCO₂ increases as additional CO₂ over that produced from metabolism is released from the HCO₃⁻ buffering of lactic acid. Because of changing [HCO₃⁻] and pH during exercise, it is inappropriate to determine ĊCO₂ from extrapolations that assume a near-linear ĊCO₂-Pco₂ relationship.

APPENDIX A

Calculating the Factors Influencing the Pco₂-Cco₂ Relationship

The following formulas for the two main factors (Fbic and Fbic) and the three subfactors of Fbic that influence the Pco₂-Cco₂ relationship were derived from Douglas’ equation (13) shown in METHODS

\[ F_{bic} = 1 + 10^{(pH - pK)} \]  

(A1)
Equation (39) is the water fraction of red blood cells (45).

Estimating the plasma [HCO₃⁻] (in mM/l blood). [HCO₃⁻]ₚ = PCO₂ × s × 10^(pH - pK₅) × (1 - Hct) (B4)

where [HCO₃⁻]ₚ is plasma [HCO₃⁻]. Estimating the red blood cell [HCO₃⁻] (in mM/l blood). [HCO₃⁻]ᵣc = PCO₂ × s × 10^(pH - pK₅) × r × Hct × 0.717 (B5)

where [HCO₃⁻]ᵣc is red blood cell [HCO₃⁻]. The r is the water fraction of plasma trapped between red blood cells, and 0.717 is the water fraction of red blood cells (45).


Equation (39) is the Donnan low of red blood cell [NH₄⁺] and SO₂ (14) as follows [NH₄⁺]ᵣc = ([HbCO₃-CO₂] + [Hbβ-Co₃-CO₂]) × SO₂ + ([Hbα-CO₂] + [Hbβ-Co₃-CO₂]) × (1 - SO₂) × Hb + 16.2

where [Hbα-CO₂] is CO₂ binding to α-NH₂ groups of the α-chain of oxyhemoglobin, [Hb- CO₂] is CO₂ binding to α-NH₂ groups of the β-chain of oxyhemoglobin, [Hbα-Co₃-CO₂] is CO₂ binding to α-NH₂ groups of the α-chain of deoxyhemoglobin, [Hbβ-Co₃-CO₂] is CO₂ binding to α-NH₂ groups of the β-chain of deoxyhemoglobin, and 16.2 converts g/dl Hb to mM.

The [Hbα-CO₂] (mM/M Hb) was calculated with the following equation (39)

[Hbα-CO₂] = 2 × λα × [CO₂]ᵣc × (1 + λα × [CO₂]ₚ) (B11)

where λα is the pH-dependent association constant of oxyhemoglobin binding to the α-NH₂ group of α-chain.

The [Hbβ-Co₃-CO₂] (mM/M Hb) was also calculated with Eq. B11, replacing λα with λβ-α, the pH-dependent association constant of deoxyhemoglobin CO₂ binding on the α-NH₂ group of α-chain.

Considering the difference of DPG (5, 22), the [Hbβ-CO₂] (mM/M Hb) was calculated from the following equation (40)


where Kp is the association constant for DPG binding to the amino groups of α-chain. In absence of CO₂, Kp’ and Kp’ are the DPG association constants when one or two CO₂ molecules, respectively, are bound, and Kp = 5,000 M⁻¹, Kp’ = 1,700 M⁻¹, and Kp’ = 500 M⁻¹ (40); [DPG] is the DPG concentration in red blood cells and is 0.88 M/M Hb in normal subjects (58); Bp is the pH-dependent association constant of oxyhemoglobin CO₂ binding on the α-NH₂ group of β-chain.

The [Hbβ-Co₃-CO₂] (mM/M Hb) was also calculated with Eq. B12, replacing λα with λβ-α, the pH-dependent association constant of deoxyhemoglobin CO₂ binding on the α-NH₂ group of α-chain.

The λ is pH-dependent association constant of Hb CO₂ binding. At pH 7.4 and 37°C, the constant values of λ series are λ₁ = 92 M⁻¹, λ₂ = 100 M⁻¹, λ₃ = 120 M⁻¹, λ₄ = 190 M⁻¹, and λ₅ = 579 M⁻¹ (39, 40). Because the λ series are pH dependent, the values used in Eqs. B11 and B12 were calculated from the following equations (39) by replacing the red blood cell [Hᵢ⁺] ([Hᵢ⁺]ₚ) at red blood cell pH 7.4 (not plasma pH) with the calculated [Hᵢ⁺]ₚ from plasma [Hᵢ⁺] ([Hᵢ⁺]ₚ)
where \( pK_c \) is the \(-\log_{10}\) values of the Hb \( \alpha\)-NH\(_2\) group CO\(_2\) binding equilibrium constants, and \( pK_z \) is the \(-\log_{10}\) values of the ionization constants of the Hb \( \alpha\)-NH\(_2\) groups (20, 43). The \([H^+]_p\) were calculated from the measured plasma pH on the assumption of a linear relationship between \(R\), which is the Donnan relationship of \([H^+]_p/[H^+]_c\), and SO\(_2\) (17)

\[
\lambda = \frac{K_c \times K_z}{K_z \times [H^+]_p + [H^+]_c} \quad (B13)
\]

where \( R^{O2} \) is for oxygenated blood and \( R^{CO} \) is for deoxygenated blood.

This study was supported in part by the Milly Liang Liu, M.D. and Steve C. K. Liu, M.D. Research Fund.

REFERENCES


