The influence of bicarbonate administration on blood pH in a "closed system": Clinical implications

An in vitro comparison was made of the effect of isotonic and hypertonic NaHCO₃ solutions on blood pH when the elimination of carbon dioxide was prevented. The results demonstrate that the rise in Pco₂, which occurs after addition of isotonic NaHCO₃, offsets the increase in bicarbonate concentration, and the rise in pH is extremely small. The addition of bicarbonate in hypertonic solutions produces a greater elevation of Pco₂ and blood pH may actually fall. The acidosis associated with hypertonicity of extracellular fluids results from the dilution of extracellular buffers and the release of protons from intracellular buffers, such as hemoglobin, in response to the increase in ionic strength.

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One of the most frequent problems among premature infants is the idiopathic respiratory distress syndrome.¹,２ As a consequence of either diffusion barriers, pulmonary hypoperfusion, or shunting mechanisms,³-⁶ inadequate ventilation results in the retention of carbon dioxide and an acute respiratory acidosis. Hypoxia often occurs in respiratory distress syndrome and some degree of metabolic acidosis secondary to the accumulation of organic acids may add to the acidemia of the syndrome. This so-called "metabolic component" is reflected by either subnormal or insufficient elevations in bicarbonate concentration appropriate for partial compensation.⁷-⁹

Attempts to correct the acidemia have included infusion of alkalinizing agents;⁰-¹³ an apparent decrease in the mortality rate in infants with respiratory distress syndrome who were treated by infusion of glucose and NaHCO₃ was initially reported by Usher.¹⁴,¹⁵ The studies of Rudolph and Yuan¹⁶ indicated that acidemia is associated with increased pulmonary vasoconstriction in calves, and the administration of alkali to correct acidemia has been proposed to improve pulmonary perfusion.³ Sodium bicarbonate is the alkali most frequently used, and the amount of bicarbonate recommended has been empirically equated to the blood pH.¹⁴,¹⁵,¹⁷,¹⁸ Rapid intravenous infusion of hypertonic...
NaHCO₃ (1.0M) has become a common practice, but this practice can be hazardous. The intravenous infusion of hypertonic solutions has been associated with tissue necrosis and thrombosis,¹⁹ hyperviscosity of the blood,²⁰ hyperosmolality of extracellular fluids with consequent acidosis,²¹-²⁴ and an increased incidence of intracranial hemorrhage.²⁵

The studies of Singer and associates²⁶ demonstrated that infusion of NaHCO₃ in normal men resulted in an immediate increase of nonmetabolic CO₂ production through the titration of protons associated with nonbicarbonate buffers according to the following reaction:

$$\text{Na}^+ + \text{HCO}_3^- + \text{HBuf} \rightarrow \text{Na}^+ + \text{Buf}^- + \text{H}_2\text{CO}_3 \quad (1)$$

$$\text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2 \quad (2)$$

The amount of nonmetabolic CO₂ recovered was equivalent to 20 per cent of the administered sodium bicarbonate when 1.2 mEq. per kilogram was rapidly infused as the 7 per cent solution. Qualitatively similar observations have been reported by Mithoefer and associates²⁷ in patients with asthma. In the clinical circumstance of impaired CO₂ excretion in severe neonatal respiratory distress syndrome, bicarbonate infusions may fail to increase pH can be deduced from equations 1 and 2, and the desired improvement in plasma pH may not occur. The failure to increase pH can be deduced from the commonly used form of the Henderson-Hasselbalch equation.

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-] \text{ mEq.}/\text{L.}}{(0.03) \text{ Pco}_2 \text{ mm. Hg}} \quad (3)$$

Since 6.1, the pK’a of the reaction, and 0.03, the conversion factor of Pco₂ from millimeters of mercury to millimoles per liter are constants, the pH varies inversely with the Pco₂ and is ultimately determined by the ratio of the concentrations of bicarbonate and carbon dioxide. Thus elevation of Pco₂ by bicarbonate infusion can offset the increase in bicarbonate concentration and the change in the concentration ratio may be so small that the blood pH remains essentially unchanged.

The present studies were performed to quantitate in vitro the influence of NaHCO₃ on blood pH when the elimination of CO₂ is prevented and to compare the responses when the bicarbonate is added either as an isotonic or hypertonic solution. The results indicate that little change occurs in blood pH and when hypertoncity is produced, it is associated with the release of additional protons from intracellular buffers of red cells, chiefly hemoglobin.

**MATERIAL AND METHODS**

**Effect of NaHCO₃ on blood pH in a closed and open system.** Twenty milliliters of heparinized cord blood were placed in each of two 50 ml. Erlenmeyer flasks. One flask was sealed with a rubber cap to prevent escape of CO₂ and the other was left open. The flasks were placed in a Dubnoff metabolic water bath and gently shaken at 37⁰ C. for 30 minutes. During this equilibration period, the sealed flask was continuously gassed with 5 per cent CO₂ in compressed air (from a storage tank) to produce an initial Pco₂ of 40 mm. Hg. After equilibration, samples were taken from each flask to measure blood pH and Pco₂. A Radiometer capillary pH meter was used for pH measurements and was standardized with a precision buffer solution of phosphate (pH = 7.383 ± 0.005 at 37⁰ C.). The Pco₂ was determined by equilibration of blood at 4.2 and 8.3 per cent CO₂ in O₂ after the technique of Astrup.²⁸ The plasma bicarbonate concentration was derived from the modified Siggaard-Andersen alignment nomogram.²⁹ A solution of 0.2N NaHCO₃ was freshly prepared and serially added to each flask in 0.1 mEq. aliquots. After each addition, the determinations of pH, Pco₂, and HCO₃⁻ concentrations were repeated. At the completion of the bicarbonate additions, the sealed flask was opened and exposed to atmospheric air for 15 minutes and the pH was again determined.

**Effect of hypertonicity on blood pH in a closed system.** Heparinized (15 ml.) cord blood was added to each of four 25 ml. Erlenmeyer flasks. All the flasks were sealed and
equilibrated for 30 minutes with 5 per cent CO₂ in compressed air at 37° C. in the Dubnoff shaker. Baseline pH, Pco₂, and [HCO₃⁻] determinations were performed and subsequently one of the following solutions was added to each flask. (1) 0.15N NaHCO₃ (244 mOsm. per kilogram of water); (2) 1.0N NaHCO₃ (1,475 mOsm. per kilogram of water); (3) 25 per cent mannitol (1,600 mOsm. per kilogram of water); and (4) 0.15N NaHCO₃ in mannitol (1,575 mOsm. per kilogram of water). The additions were made in 0.1 mEq. aliquots of bicarbonate and the volume of mannitol added (solution 3) was equal to that of the bicarbonate in mannitol solution (solution 4). The pH, Pco₂ and [HCO₃⁻] determinations were repeated after each addition.

The relative effects of acute dilution by isotonic and hypertonic solutions on blood pH were evaluated as follows: 10 ml. of fetal cord blood containing 13.2 Gm. per 100 ml. of hemoglobin was each added to two sealed 25 ml. Erlenmeyer flasks. The flasks were incubated in a Dubnoff water bath for 30 minutes at 37° C. and gassed with 5 per cent CO₂ in compressed air. Base-line blood pH, Pco₂, and HCO₃⁻ concentrations were determined. Intracellular red cell pH was measured on frozen and thawed samples of red cells after anaerobic separation of the serum in capillary hematocrit tubes. After the base-line measurements, 0.5 ml. of either 0.9 per cent NaCl (302 mOsm. per kilogram of water) or 25 per cent mannitol (1,600 mOsm. per kilogram of water) was added to each flask. The determinations of plasma pH, Pco₂ and [HCO₃⁻] were repeated as well as the intracellular red cell pH. The osmolalities of the plasma and stock solutions were determined by vapor pressure osmometry without dilution.

The titration of hemoglobin in solutions of different ionic strengths. A solution of fetal hemoglobin (9.0 Gm. per 100 ml.) was prepared by osmotic hemolysis in distilled water from packed fetal erythrocytes obtained from cord blood. Three 10 ml. solutions of 0.90 Gm. per 100 ml. fetal hemoglobin of different ionic strengths were subsequently prepared by diluting 1 ml. of the 9.0 Gm. per cent fetal hemoglobin solution with 9 ml. of either distilled water, 0.15N KCl, or 0.300N KCl to a final volume of 10 ml. After initial pH measurement, 5 ml. of each hemoglobin solution was titrated with 0.01N HCl and the remaining 5 ml., with 0.01N NaOH. The titrations were performed with an external combination-type glass electrode connected to a Beckman GS pH meter.

The partial titration curve of hemoglobin at different ionic strengths was analyzed in greater detail from pH 6.5 to 8.0. Three 10 ml. solutions of fetal hemoglobin (0.95 Gm. per 100 ml.) were prepared as above and the ionic strength was increased by dilution with 0.15 and 0.45M KCl solutions. The influence of ionic strength and osmolality on the titration curves was also studied by titrations of hemoglobin solutions diluted in 0.30M urea.

**RESULTS**

Typical results from six experiments which demonstrate the effect of isotonic NaHCO₃ addition to blood in a sealed and open system are shown in Fig. 1. In the sealed flasks initial values were: pH = 7.320, Pco₂ = 41 mm. Hg, and [HCO₃⁻] = 20.7 mEq. per liter. After serial addition of five 0.1 mEq. aliquots of NaHCO₃ the pH had only risen to 7.415, and the Pco₂ rose from 41 to 70 mm. Hg. In contrast, the addition of equivalent amounts of NaHCO₃ to blood in the open system was associated with a rise in pH from 7.78 to 8.66. When the sealed system was opened and the CO₂ allowed to escape, the pH of the blood promptly rose to 8.65, comparable to the final pH of the blood in the open system. It is of interest that when the amount of NaHCO₃ added was equal to the pre-existing bicarbonate content (arrow in Fig. 1), the pH in the sealed flask had risen by only 0.040 units.

Representative results from three experiments which illustrate the influence of hypertonicity on plasma pH in a sealed system are
shown in Fig. 2. The blood in the four flasks had identical pH and Pco₂ values after the initial equilibration with the 5 per cent CO₂ gas mixture. Five serial additions of 0.1 mEq. aliquots of 0.15N NaHCO₃ and 1.0N NaHCO₃ were associated with a small rise in pH from 7.245 to 7.355 and 7.395, respectively. The slightly greater rise of pH in the flask to which 1.0N NaHCO₃ was added can be attributed to a smaller dilution of the plasma since seven times the volume of the isotonic bicarbonate solution was required to achieve the bicarbonate equivalent to the 1.0N NaHCO₃ solution. When a volume of 0.15N NaHCO₃ in mannitol (1,575 mOsm. per kilogram of water) was added, the plasma pH actually fell from 7.245 to 7.215, and when 25 per cent mannitol alone was used, the plasma pH fell from 7.245 to 6.90.

The Pco₂ rose in all of the flasks to which bicarbonate was added and the amount of CO₂ generated was related to the osmolality and pH of the plasma. Of particular interest was the elevation in Pco₂ from 36 to 57 mm Hg and the fall in pH in the blood sample to which only mannitol had been added. This observation was studied in greater detail.

Table I lists representative results from five experiments in which the changes of plasma pH in sealed flasks were measured after dilution of the blood samples with isotonic saline and hypertonic mannitol. The addition of equal volumes of saline and mannitol resulted in a greater fall in plasma pH and bicarbonate with the mannitol solution. These results could be explained in part by
Table I. The response of plasma pH to the dilution of blood with isotonic and hypertonic solutions

<table>
<thead>
<tr>
<th>Period</th>
<th>Flask 1</th>
<th>Flask 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Equilibration of 10 ml. of cord blood with 5% CO₂ in air</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.230</td>
<td>7.230</td>
</tr>
<tr>
<td>pH₅⁺</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Pco₂</td>
<td>16.3</td>
<td>16.3</td>
</tr>
<tr>
<td>[HCO₃⁻] (mEq./L.) plasma</td>
<td>7.03</td>
<td>7.04</td>
</tr>
<tr>
<td>pH₅⁺</td>
<td>293</td>
<td>293</td>
</tr>
<tr>
<td>Osm. (mOsm./Kg.H₂O)</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Addition</td>
<td>0.5 ml. 0.9% NaCl (302 mOsm./Kg.H₂O)</td>
<td>0.5 ml. 25% mannitol (1575 mOsm./Kg.H₂O)</td>
</tr>
<tr>
<td>pH₅⁺</td>
<td>7.220</td>
<td>7.115</td>
</tr>
<tr>
<td>Pco₂</td>
<td>15.7</td>
<td>14.3</td>
</tr>
<tr>
<td>[HCO₃⁻]</td>
<td>7.04</td>
<td>7.07</td>
</tr>
<tr>
<td>pH₅⁺</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>Osm</td>
<td>302</td>
<td>365</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Addition</td>
<td>0.5 ml. 0.9% NaCl (302 mOsm./Kg.H₂O)</td>
<td></td>
</tr>
<tr>
<td>pH₅⁺</td>
<td>7.210</td>
<td></td>
</tr>
<tr>
<td>Pco₂</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>[HCO₃⁻]</td>
<td>7.05</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*E = extracellular, I = intracellular.

an osmotic movement of bicarbonate poor intracellular fluid into the plasma in response to the hypertonicity of mannitol. However, by further addition of saline to expand extracellular volume in the isotonic flask to a comparable hematocrit, the plasma pH and bicarbonate concentrations were distinctly lower in the mannitol flask (pH 7.115 versus pH 7.210).

The change in intracellular pH of the red cell could not account for the reduction in extracellular pH and bicarbonate concentration in the samples to which mannitol was added. The reduction in bicarbonate concentration of the plasma in the flask to which saline was added was consistent with simple dilution of the extracellular bicarbonate without change in Pco₂. What was unique to the mannitol addition was the rise of Pco₂ without change in Pco₂. What was unique to the mannitol addition was the rise of Pco₂ of 6 mm. Hg indicating the generation of extra H⁺ ions in the blood.

When these same experiments were performed using plasma alone, a rise in Pco₂ was not observed, and the bicarbonate dilution and fall in pH were almost identical with either mannitol or saline as the diluent. The difference between whole blood and plasma indicated that the protons generated in response to the hypertonicity and reflected by the elevation in Pco₂ originated from within the red cells. From the rise in Pco₂ associated with the addition of hypertonic mannitol to blood, one can estimate those protons that were generated and titrated by the pre-existent bicarbonate by equating the change in Pco₂ to the millimoles of (H⁺) neutralized. *

\[ \Delta [\text{CO}_3^-] = 0.03 \times \Delta \text{Pco}_2 \text{ mm. Hg} \]
\[ 0.03 \times 6 = 0.18 \text{ mEq./L.} \]

If \( \Delta [\text{CO}_3^-] = [\text{H}^+] \), then 0.18 mEq. per

*The total change in (H⁺) is only partly reflected by the change in Pco₂, because all of the blood buffers participate in changes of acid-base equilibrium. This ordinarily could be quantitated from the change in "buffer base" or "base excess." However, these nomogram interpolations are standardized at normal ionic strengths of the blood. In the present study the ionic strength of the intracellular fluid was increased while that in the plasma was reduced when mannitol was added. Therefore the titration curve of these whole blood samples could not be derived from the nomogram for buffer base or base excess.
liter of H⁺ was generated and subsequently neutralized by the pre-existent plasma bicarbonate. Since hemoglobin is the major buffer of the erythrocyte, the protons generated were related to the hemoglobin content of the blood.

$$1.8 \times 10^{-2} \text{ mEq. } H^+ / L_0 = 1.8 \times 10^{-3} \text{ mEq. } H^+ \text{ in 10 ml. blood}$$

$$1.8 \times 10^{-3} \text{ mEq. } H^+ / 1.32 \text{ Gm. hemoglobin} = 2.1 \times 10^{-3} \text{ mEq.}$$

H⁺/Gm. hemoglobin or

$$\left(2.3 \times 10^{-2} \text{ mEq. } H^+\right) / \text{mMoles hemoglobin}$$

If one assumes that no shift in bicarbonate occurred between cells and plasma, the calculation of the difference in plasma bicarbonate in the flasks before and after addition of 0.5 ml. of mannitol indicate a $\Delta$($\text{HCO}_3^-$) of $1.39 \times 10^{-3} \text{ mm}$, which is of the same order of magnitude as the change in $P_{\text{CO}_2}$ concentration.

To verify that an increase in ionic strength of the intraerythrocyte fluid secondary to hypertonicity is associated with the release of protons from hemoglobin, titration curves of hemoglobin were performed in solutions whose ionic strengths were increased by the addition of KCl. The titration curves (Fig. 3) demonstrate that as the ionic strength was increased, hemoglobin became a stronger acid above pH 7.0 in that more alkali was necessary to raise the pH.

The titration curve of hemoglobin in a solution whose osmolality was increased to 270 mOsm. per kilogram of water by the addition of urea, was identical to the titration curve of hemoglobin in distilled water. The release of protons from hemoglobin was therefore a response to increasing ionic strength rather than to osmolality per se. An estimate of the release of protons from hemoglobin in response to increased ionic strength was derived from the more detailed titration curves of hemoglobin in Fig. 4.

The pH of the original hemoglobin solution (0.95 Gm. per cent) in distilled water was pH 7.22. The pH of the solution of hemoglobin in 135 mEq. per liter of KCl was 7.10; in 405 mEq. per liter of KCl the pH was 7.08. Restoration of the latter two hemoglobin solutions to pH 7.22 required the addition of 0.040 ml. and 0.050 ml. of 0.01N NaOH, respectively.

The difference represents 0.010 ml. x 0.01N = $1.0 \times 10^{-4} \text{ mEq. of } H^+ \text{ in the 5 ml. of 0.95 Gm. per 100 ml. hemoglobin solution. Thus}$

$$1.0 \times 10^{-4} \text{ mEq. } H^+ / 4.75 \times 10^{-2} \text{ Gm. hemoglobin} = 1.4 \times 10^{-3} \text{ mEq. } H^+ / \text{Gm. hemoglobin}$$

This value approximated the proton generation (1.4 $\times 10^{-3} \text{ mEq. } H^+ \text{ per Gm. hemoglobin}$) calculated from the change in $P_{\text{CO}_2}$ after addition of hypertonic mannitol (Table I).

**DISCUSSION**

The quantitative importance of the bicarbonate system in the regulation of pH in extracellular fluids at pH 7.4 is not simply due to its capacity as a buffer. At pH 7.4, the molar concentration ratio of [HCO₃⁻]/$P_{\text{CO}_2}$ is 20:1 whereas the maximum capacity of a buffer to minimize changes in pH occurs when the concentration ratio of the acid and
its dissociated anion is 1:1. For the bicarbonate system, this optimal ratio is at pH 6.1. At pH 7.4, the efficiency of the bicarbonate system depends upon the fact that the acid form of the buffer, \( \text{H}_2\text{CO}_3 \), dissociates into water and the volatile gas, \( \text{CO}_2 \); the concentration of the latter is independently regulated by the respiratory system. More recent reviews of the chemistry of carbonic acid have emphasized that the molecular species, \( \text{H}_2\text{CO}_3 \), is a relatively strong acid with a pKa of 3.6 comparable to acetic and lactic acids. It should be realized that the denominator of the mass action law (equation 3) refers to all nonbicarbonate \( \text{CO}_2 \), which includes dissolved \( \text{CO}_2 \) and \( \text{H}_2\text{CO}_3 \). The dissolved \( \text{CO}_2 \) is not an acid and is in a concentration 400 to 700 times greater than the actual \( \text{H}_2\text{CO}_3 \). Thus the pK'a of 6.1 in equation 3 is a composite factor that combines the dissociation constants of the acid, \( \text{H}_2\text{CO}_3 \), and the equilibrium constant of the hydration of carbon dioxide. The latter constant indicates that fraction of dissolved carbon dioxide which is combined with water as \( \text{H}_2\text{CO}_3 \).

The present studies illustrated the inefficiency of sodium bicarbonate to increase blood pH when the \( \text{CO}_2 \) formed from the titration by bicarbonate of protons, according to equations (1) and (2), is not permitted to escape (Fig. 1). In the sealed flasks, the generation of \( \text{CO}_2 \), although small relative to the change in bicarbonate concentration, was sufficient to offset any significant elevation in the concentration ratio; consequently, very little rise in pH occurred.

The in vitro comparison of hypertonic and isotonic sodium bicarbonate solutions in the correction of acidosis demonstrated the disadvantage in the use of hypertonic sodium bicarbonate. The elevation of \( \text{Pco}_2 \) that occurred in the sealed flasks (Fig. 2) when sodium bicarbonate was added as a 1.0N solution was considerably greater than when equivalent amounts of bicarbonate were added as an isotonic solution. The additions of 0.15N \( \text{NaHCO}_3 \) in mannitol was associated with an actual fall in pH, despite the fact that a solution containing 150 mEq. per liter of \( \text{HCO}_3^- \) was added to blood with an initial plasma concentration of 15 mEq. per liter of \( \text{HCO}_3^- \). This paradoxical fall in pH could be explained by the effect of hyperosmolality on blood as shown in Table I and Fig. 2, when mannitol alone was added to blood. The rise in \( \text{Pco}_2 \), which occurred despite the fact that no bicarbonate was added to the system, implies that the \( \text{CO}_2 \) generated must have arisen from the titration of pre-existent bicarbonate by extra protons generated in response to hypertonicity. The addition of hypertonic solutions to blood, which are restricted to extracellular fluid, causes an osmotic flow of bicarbonate-poor water out of the red cells. This loss in water increases the ionic strength of the electrolytes within the erythrocytes. One result is that hemoglobin, the major weak acid buffer of red cells, dissociates more readily in accordance with the theory of Debye-Hückel (that weak acids increase their dissociation constants (lower

![Fig. 4. Partial titration curve of 0.95 Gm. per cent fetal hemoglobin solution at different ionic strengths. The pH of the hemoglobin solution in distilled water was 7.22. Increasing the ionic strength to 0.135 and 0.405 required the addition of 0.04 and 0.05 ml. of 0.01N NaOH, respectively, to restore the pH to 7.22. The titration curve of hemoglobin in 0.27M urea was the same as that in distilled water.](image-url)
their pK a) in proportion to the square root of the ionic strength). Such a relationship was demonstrated by Hastings and associates for carbonic acid; the present results of the titration curves of hemoglobin indicate that hemoglobin behaves in a similar manner. The extra protons generated in response to the increase in ionic strength titrated the pre-existent bicarbonate of the blood and led to the formation of CO₂, according to the following reactions:

\[ \text{HBuf} \xrightarrow{\text{ionic strength}} \text{H}^+ + \text{Buf}^- \] (4)
\[ \text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}_2\text{O} + \text{CO}_2 \uparrow \] (2)

It is the increase in ionic strength and not hyperosmolality per se, that initiates reaction 4, since the addition of mannitol to plasma did not produce the same result, and addition of urea did not influence the hemoglobin titration curves.

The acute in vivo expansion of extracellular fluid with neutral isotonic solutions results in acidosis, which is ascribed principally to the dilution of extracellular bicarbonate in the presence of a constant Pco₂. Most investigators have also attributed the acidosis associated with hypertonicity as secondary to this dilution, since with hypertonic solutions involving a nonpermeant solute there is an additional dilution of extracellular bicarbonate by the osmotic flow of bicarbonate-poor water from intracellular fluid to the extracellular space in order to restore osmotic equilibrium. However, Sotos and associates indicated that hypertonicity of extracellular fluid was also associated with the release of intracellular acids to extracellular fluid. Their interpretation has been questioned because the animals became hypotensive, and increased organic acid production may have resulted from hypoperfusion of the tissues. The present in vitro study (Fig. 2 and Table I) indicated that the acidosis secondary to hypertonicity involves not only a simple dilution of extracellular bicarbonate in which the Δ pH could be predicted from equation 3, but also includes the titration of previously existent bicarbonate by protons newly released from such intracellular buffers as hemoglobin in response to the increase in ionic strength (equation 4). Actually, the experiments of Winters and associates and Makoff and co-workers reflect this distinction. In their in vivo studies, Pco₂ was maintained constant by artificial ventilation; hence, any increase in CO₂ was not evident. However, the change in buffer base of the blood indicated an unexplained loss in extracellular bicarbonate. It is likely this loss of bicarbonate resulted from the release of previously bound protons that titrated pre-existent bicarbonate and was expired as CO₂ according to reaction 4. Whether intracellular buffers other than hemoglobin respond similarly is not known, but the regulation of intracellular pH involves many metabolic processes that influence acid production.

It can be argued that the present in vitro results are not directly applicable to infants with respiratory distress syndrome, because the nonmetabolic CO₂ that is generated from the infused bicarbonate would be excreted unless the infant was apneic or in cardiac arrest. This would explain why many infants with respiratory acidosis, if given sufficient amounts of bicarbonate, do show a small rise in plasma pH. However, if it is not possible to increase the tidal volume of the infant, the elevation in Pco₂ secondary to the infusion of bicarbonate may be prolonged and minimize the rise in pH as was seen in the response of the infant (Table II) with severe respiratory distress syndrome documented at autopsy.

The bicarbonate solution was infused through an umbilical vein catheter over 2 hours and the blood chemical values were determined on arterialized capillary blood samples from the fingers of the right hand. Despite the elevation of 7 mEq per liter in the plasma bicarbonate, there was a concomitant rise in the Pco₂ and the plasma pH remained unchanged. Although several other reports have recorded variable increases in plasma pH after infusion of NaHCO₃ to infants with respiratory distress syndrome, a frequent occurrence has been the prolonged and even marked elevation of Pco₂.
Table II. Patient B. B. F. (JHH 134-82-15)

<table>
<thead>
<tr>
<th>Time (hr.)</th>
<th>P&lt;sub&gt;co2&lt;/sub&gt; (mm. Hg)</th>
<th>[HCO&lt;sub&gt;3&lt;/sub&gt;]&lt;sub&gt;-&lt;/sub&gt; (mEq./L)</th>
<th>Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.13</td>
<td>35</td>
<td>11.3</td>
</tr>
<tr>
<td>2</td>
<td>7.12</td>
<td>59</td>
<td>18.0</td>
</tr>
</tbody>
</table>

42, 43 The combination of CO<sub>2</sub> production from continuing metabolism of at least the basal rate of 0.3 mM per kilogram per minute<sup>44, 45</sup> and the simultaneous generation of nonmetabolic CO<sub>2</sub> originating from the titration of protons by the infused bicarbonate may exceed the ventilatory capacity of the lungs and result in significant CO<sub>2</sub> retention. Since there is a more rapid equilibration of CO<sub>2</sub> across cell membranes and the blood-brain barrier than the compensatory increase in bicarbonate ion, the acute hypercapnia creates a paradoxical lowering of pH in the cerebrospinal fluid.<sup>46, 47</sup> The lowering of spinal fluid pH is believed to be associated with central nervous system depression that may further interfere with the respiratory efforts of the infant to eliminate CO<sub>2</sub>.

These in vitro studies suggest that the use of sodium bicarbonate to correct acidemia will not be effective if a prompt increase in CO<sub>2</sub> excretion cannot be assured, since the capacity of bicarbonate to alkalinize blood depends on the elimination of the CO<sub>2</sub> produced. If the latter pathway is obstructed, unphysiologically large amount of NaHCO<sub>3</sub> would be required to achieve even a small rise in plasma pH. The use of hypertonic solutions not only invokes the hazards of hyperosmolality, but the acidemia may become aggravated from the dilution of extracellular buffers and the dissociation of protons from intracellular buffers in response to the increased ionic strength.

REFERENCES

18. Nelson, W. E., Vaughan, V. C., III, and


Erratum. In the article, “The influence of bicarbonate administration on blood pH in a “closed system”: Clinical implications,” by E. M. Ostrea, Jr., and G. B. Odell, which appeared on pp. 671-680 of the April, 1972, issue of the Journal, line 11 in the second paragraph on p. 672 should have read: further increase the already elevated Pco₂.