What is the ultimate goal in acid-base regulation?

Selvakumar Balakrishnan,① Maya Gopalakrishnan,① Murali Alagesan,② and E. Sankaranarayanan Prakash②

①Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India; and ②School of Medicine, Faculty of Medical and Health Sciences, Asian Institute of Medicine, Science, and Technology, Sungai Petani, Kedah Darul Aman, Malaysia

Submitted 17 February 2006; accepted in final form 2 December 2006

Balakrishnan S, Gopalakrishnan M, Alagesan M, Prakash ES.
What is the ultimate goal in acid-base regulation? Adv Physiol Educ 31: 51–54, 2007; doi:10.1152/advan.00010.2006.—It is common to see chapters on acid-base physiology state that the goal of acid-base regulatory mechanisms is to maintain the pH of arterial plasma and not arterial PCO2 (PaCO2) or plasma HCO3. A hypothetical situation in which the PaCO2 of arterial plasma is 80 mmHg and the plasma HCO3 concentration is 48 mM is presented and analyzed to get over this misconception. As per the modified Henderson equation, the pH of arterial plasma would be 7.4; however, we explain that this may be associated with intracellular acidosis due to intracellular hypercapnia and that derangement of homeostasis is evident from the occurrence of respiratory depression and, eventually, coma in the patient described. This suggests that the ultimate goal of acid-base regulatory mechanisms is not just the maintenance of the pH of arterial plasma but the maintenance of the steady-state pH of intracellular fluid as well.

Acidosis; intracellular pH; homeostasis

It is common to see chapters on acid-base physiology state that the goal of acid-base regulatory mechanisms is to maintain the pH of arterial plasma and not arterial PCO2 (PaCO2) or plasma HCO3. A hypothetical situation in which the PaCO2 of arterial plasma is 80 mmHg and the plasma HCO3 concentration is 48 mM is presented and analyzed to get over this misconception. As per the modified Henderson equation, the pH of arterial plasma would be 7.4; however, we explain that this may be associated with intracellular acidosis due to intracellular hypercapnia and that derangement of homeostasis is evident from the occurrence of respiratory depression and, eventually, coma in the patient described. This suggests that the ultimate goal of acid-base regulatory mechanisms is not just the maintenance of the pH of arterial plasma but the maintenance of the steady-state pH of intracellular fluid as well.

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Of the 17 students, 4 students chose option A and 8 students chose option B, but only 2 students chose option D, the answer that we contend is the best. The above problem was discussed (using PowerPoint slides) by S. Balakrishnan, a first-year undergraduate medical student. Questions were invited as the presentation occurred. The problem was analyzed and discussed as follows.

\[ \text{PaCO}_2 / \text{HCO}_3 = 80/48 = 1.6 \]

According to the Henderson equation (2), which is \([H^+] (\text{in nM}) = 24 \times \text{PaCO}_2 / \text{HCO}_3 (\text{in mM})\), we find that in this case, the \([H^+] \) of arterial plasma equals 40 nM (a pH of 7.4), i.e., normal. Both PaCO2 and HCO3 are increased from their normal values; however, it cannot be said from the data provided which is the primary disturbance since both have increased to the same extent from their normal values. Thus, although the pH of arterial plasma is normal, there is an excess of CO2 as well as HCO3 in arterial plasma. We may call it a mixed acid-base disturbance. This apart, let us think of a real-life situation in which this might possibly happen. Consider a 60-yr-old smoker with an acute exacerbation of preexisting moderate-severe chronic obstructive lung disease. The patient would be expected to be chronically hypercapnic (say, with a PaCO2 of ~60 mmHg) in the first place. An acute exacerbation due to a lower respiratory tract infection could cause PaCO2 to increase to 80 mmHg from 60 mmHg. It is important to realize that the source of the culprit acid CO2 is the cell itself (schematized in Fig. 1), i.e., more CO2 is produced as a result of an augmentation in the metabolic rate in the context of an infection, to the point that the respiratory center is acutely depressed. Because minute ventilation is compromised, the elimination of CO2 does not match the production. Therefore, the increased PaCO2 (80 mmHg here) reflects the fact that CO2 accumulates mainly inside cells. A summary of this sequence of events is shown in Fig. 2. When there is an excess of CO2, most of the buffering occurs inside cells (4). We assume that this patient also has severe vomiting due to some other reason, and, as a result of that, acid is lost from the extracellular fluid (ECF) to eventually cause arterial plasma HCO3 levels to increase to the hypothetical value of 48 mM mentioned here. The patient slips into a coma. Why this problem when the arterial plasma pH is 7.4, i.e., normal? A key question is whether there is any abnormality in intracellular pH. Evidently, the H ions formed from CO2 would be buffered by nonbicarbonate buffers in the intracellular fluid (ICF) as well as the ECF. However, a state would be reached when the concentration gradient that promotes exit of CO2 from cells is abolished and the buffering capacity of intracellular buffers is exceeded, and the first deviation from normal would be a drop in intracellular pH below normal due to intracellular hypercapnia. We imagine that the resulting drop in ECF pH is counterbalanced by an increase in pH caused by...
an increase in plasma [HCO₃⁻] due to vomiting. In the new steady state that is eventually attained and at which point this patient's arterial blood has been analyzed, PaCO₂ is 80 mmHg, arterial plasma [HCO₃⁻] is 48 mM, and the pH of arterial plasma is 7.4. However, the intracellular pH is well below normal. The low intracellular pH may at least in part explain why the patient is comatose. Hypercapnia depresses the level of consciousness in proportion to the rate of rise of PaCO₂ (5). Of course, this would have been compounded by arterial hypoxemia (which always accompanies CO₂ retention due to alveolar hypoventilation), hypovolemia, and electrolyte abnormalities associated with vomiting. However, it is clear that it is not adequate to maintain arterial plasma pH alone but intracellular pH would also have to be maintained within normal limits. Indeed, intracellular pH is regulated by several mechanisms, as detailed in Ref. 2; for example, the Na-H antiport is an acid extruder that extrudes H ions in the face of intracellular acidosis. These transporters are sensitive to primary changes in ICF pH and ECF pH. Therefore, we think that the single best answer for the problem is option D. However, the extent to which the intracellular pH declines in different tissues depends on several factors including buffering power and the complement and kinetics of acid-base regulatory mechanisms, and all of these are known to differ at least to some extent between tissues. In this context, in the problem described above, it is impossible to tell that the steady-state intracellular pH will be low in all cells. Therefore, given the power of intracellular pH defense mechanisms, it is possible that the steady-state intracellular pH might be normal or even greater than normal at least in some tissues.

Let us now answer the following question: How should we treat this patient?

A. Add metabolic acid to plasma.
B. Remove CO₂ from plasma.
C. Administer NaHCO₃.

As treatment would have to address the primary disturbance, i.e., intracellular acidosis due to accumulation of CO₂, slow removal of CO₂ from plasma by mechanical ventilation seems the most appropriate strategy since this would allow CO₂, the culprit in question, to pass down its concentration gradient from the ICF to ECF and then be eliminated. On the other hand, adding metabolic acid to plasma would prevent the exit of CO₂ from cells by acidifying plasma. The administration of NaHCO₃ alone will not help because HCO₃ cannot buffer H ions formed from CO₂. Another question was then asked: Which acid-base disturbance would become apparent as the patient is treated this way, i.e., by mechanical ventilation?

A. Respiratory acidosis.
B. Metabolic acidosis.
C. Metabolic alkalosis.
D. Respiratory alkalosis.

Many students quickly responded by saying metabolic acidosis. The presenter also discussed how metabolic alkalosis could be managed. In the first place, metabolic alkalosis occurred as a result of vomiting; and, therefore, replenishing the ECF volume with isotonic NaCl would be the primary treatment strategy (3). However, it is important to understand that the alkalosis is to a significant extent due to avid reabsorption of Na, Cl, and HCO₃ by the kidneys. Note that the kidneys conserve HCO₃ in the face of volume depletion even if arterial pH is above normal (3). Of course, arterial blood should be sampled more frequently and PaCO₂ and [HCO₃⁻] determined. Importantly, the patient’s ability to breathe on his own (without the ventilator) and eliminate CO₂ as well as his kidneys’ ability to excrete excess HCO₃ must be assessed.

To summarize, the problem discussed here offers interesting insights into the ultimate goal of acid-base regulatory mechanisms. First, there may be an acid-base disorder even if the arterial plasma pH is above normal (3). Thus, the ultimate goal of acid-base regulatory mechanisms is not just the maintenance of pH of arterial plasma but also the maintenance of pH of the ICF. That is the teaching point here. This makes sense because metabolic reactions, the enzymes that catalyze them, nucleic acids, and proteins are all exquisitely sensitive to pH changes and work well at an optimum pH.

Furthermore, it appears that when steady-state PaCO₂ and [HCO₃⁻] are 40 mmHg and 24 mM, respectively, not only is arterial plasma pH normal but the pH of the ICF would also be normal. Could there be an exception to this assumption? To answer this question, we refer to an interesting hypothetical situation described by DuBose (3): i.e., a patient with diabetic ketoacidosis (the source of the ketoacids is from only within liver cells but not other tissues) also has severe vomiting due to some other cause. For the sake of an argument, we assume that the fall in plasma [HCO₃⁻] as a result of ketoacidosis is equal to the gain of [HCO₃⁻] due to vomiting and that both processes are occurring nearly simultaneously; the resulting steady-state [HCO₃⁻] of arterial plasma is 24 mM with no changes in arterial plasma pH and, therefore, no changes in ventilatory drive. Thus, PaCO₂ remains at 40 mmHg. To summarize, this is a situation in which PaCO₂ = 40 mmHg, arterial plasma [HCO₃⁻] = 24 mM, and arterial plasma pH = 7.4. If we imagine that the rate at which the ketoacids are produced in liver cells exceeds the rate at which they are utilized in other tissues and that ketoacids accumulate in the liver to the extent that they exceed the buffering power, there would be an acid-base disturbance, i.e., intracellular ketoacidosis, at least in liver cells. The author rightly suggests that the presence of an elevated anion gap may point to the presence of intracellular metabolic acidosis; however, in some instances, the anion gap may also be normal (3). First, this illustration (which was not part of the classroom discussion because we thought about it only during the revision of this manuscript) reinforces the central concept we wish to highlight in this article, i.e., the ultimate goal of acid-base regulatory mechanisms would be to maintain the pH of the ICF as well as the ECF. More importantly, from a clinical point of view, it demonstrates that the assessment of intracellular acid-base status from arterial plasma pH, PaCO₂, and plasma [HCO₃⁻] values alone may sometimes be misleading, especially in the absence of a well-taken history.

From the above discussion, it is necessary to clarify that the statement “the core of the problem is not buffer base or fixed cation or the like but simply the maintenance of the H⁺ concentration of the ECF” (4) is somewhat misleading. The above statement seems to have been made in the context of a discussion of the regulation of the pH of the ECF; however, from the examples used here, it is clear that the plasma pH per se does not always accurately mirror the intracellular acid-base balance. Therefore, we suggest that it helps to state explicitly that all acid-base regulatory mechanisms are geared toward maintaining the steady-state pH of all body fluids within normal limits, and this would also cause PaCO₂ and arterial plasma [HCO₃⁻] to be 40 mmHg and 24 mM, respectively.

It is worth mentioning that this teaching point can also be gathered from problems on mixed acid-base disturbances commonly presented in textbooks. However, in those instances, mixed acid-base disturbances cannot be diagnosed without the use of difficult-to-memorize equations to calculate the values of “expected PaCO₂” and “expected HCO₃⁻”, as detailed in Ref. 3 but not invoked here. To teach this very important concept to first-year medical students, the hypothetical problems presented in this article seem appropriate. They may also be used to set the stage for a discussion of mixed acid-base disturbances. These problems may also be used as a prelude to a discussion of mechanisms regulating intracellular pH.

The following multiple-choice question was used to test students’ understanding of the concept presented in the session.

**Choose the single best answer:**

Consider the hypothetical situation: PaCO₂ = 20 mmHg and arterial plasma [HCO₃⁻] = 12 mM. Which of the following statements is correct?

<table>
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<tr>
<th>Table 1. Students’ rating of the presentation</th>
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<tr>
<td>Rating</td>
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<tr>
<td>Overall rating of the presentation</td>
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<tr>
<td>How satisfied are you that you learned something you did not know before?</td>
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<tr>
<td>How much do you think that the concepts presented today will influence your analysis of disorders of acid-base regulation?</td>
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\( n = 17 \) students that rated the presentation. The rating scale was 1–5, with 1 being the lowest and 5 the highest.
A. Metabolic acidosis is the primary acid-base disturbance.
B. Respiratory alkalosis is the primary acid-base disturbance.
C. Intracellular pH is lower than normal.
D. Intracellular pH is higher than normal.
E. There is no acid-base disturbance.

Sixteen of seventeen students chose option D, the answer most likely to be correct. The concern that intracellular pH may be near normal at least in some cells applies equally well to this problem. Students’ ratings of the session are shown in Table 1. Regarding classroom dynamics, we observed that almost all students spoke sometime during the session and asked questions about the patient as they tried solving it on their own. A point that often surfaced was that there was a need to continually track arterial pH, plasma HCO$_3^-$, and Pa$_{CO_2}$, i.e., there was a lot of discussion regarding dynamic and steady states, quite germane to the problem presented here. At the end, students rated the presentation (shown in Table 1), and written comments were also solicited. It is worth noting that the presenter, S. Balakrishnan, a first-year undergraduate student, was reviewed by his peers and defended most of the queries with some support from his teacher, E. S. Prakash. More importantly, a lively discussion occurred among the students themselves. While one of the participants complemented S. Balakrishnan’s presentation by describing it as elegant and imaginative, another humbly suggested “Please accept if you are not able to justify your point.” The entire session lasted ~1 h.

The reader is referred to an excellent review article by Boron (1), in which the author suggests a simple approach to understanding the basic mechanisms involved in the regulation of intracellular pH.

ACKNOWLEDGMENTS

The authors are grateful to the students who participated in the classroom session narrated here.

REFERENCES