Winters's formula revisited

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ABSTRACT

The fundamentals of acid-base physiology underlie numerous pathological processes and treatments. The modern methods used to evaluate a patient's acid-base status are based on Lawrence J. Henderson's early work on the thermodynamics and kinetics of acid-base reactions. Henderson's work eventually culminated in two groundbreaking papers advancing our understanding and approaches to measuring a patient's acid-base status. However, Henderson's formula failed to provide information on the secondary compensation to primary acid-base disturbances. During the mid-20th century, two physicians, Horace W. Davenport and Robert W. Winters, revealed the physiological mechanisms and provided a mathematical description of acid-base physiology. In this paper, we discuss the history of acid-base physiology and revisit Winters's formula with respect to extreme disturbances in pH.

Keywords: Lawrence Henderson, Horace Davenport, Robert Winters, Henderson-Hasselbalch equation, acid-base physiology, Winters's formula, and Davenport diagrams

INTRODUCTION

The fundamentals of acid-base physiology underlie numerous pathological processes and treatments taught throughout medical education and used in practice.[1] Extreme disturbances in pH are regularly encountered with acute conditions, such as such as acute respiratory failure, diabetic ketoacidosis, and acute renal failure.[2] The modern methods used to evaluate a patient's acid-base status are based on Lawrence J. Henderson's early work on the thermodynamics and kinetics of acid-base reactions.[1,3] Henderson published two groundbreaking papers in the *American Journal of Physiology* summarizing this relationship in the equation known as the Henderson-Hasselbalch Equation (HHE) as shown below.[3–5]

$$pH = pK + \log\left(\frac{[A^-]}{[HA]}\right) \qquad \text{(Eq 1)}$$

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where pK is defined as the $-\log(K_{H^+_{dissociation}})$, and [HA] and [$A^-$] represent the concentrations of weak acid and anion base, respectively. Fundamentally, the HHE is derived by rewriting the mass action expression of acid-base dissociation into logarithmic form:

$$HA \leftrightarrow H^+ + A^- \qquad \text{(Eq 2)}$$

$$K = \frac{[H^+][A^-]}{[HA]} \qquad \text{(Eq 3)}$$

$$\log(K) = \log([H^+]) + \log\left(\frac{[A^-]}{[HA]}\right) \qquad \text{(Eq 4)}$$

$$-\log([H^+]) = -\log(K) + \log\left(\frac{[A^-]}{[HA]}\right) \qquad \text{(Eq 5)}$$

$$pH = pK + \log\left(\frac{[A^-]}{[HA]}\right) \qquad \text{(Eq 6)}$$

where K is the rate of dissociation, and [HA] and [A^-] represent the concentrations of weak acid and anion base, respectively.[4] Before the Henderson-Hasselbach equation, the law of mass action was applied to understand

various chemical phenomenon observed during the 19th century. Specifically, "the law of mass action had been formulated in 1864 by two Norwegian brothers-in-law, Peter Waage (1833–1900) and Cato Maximillian Guldberg (1836–1902), but it fell to a medical doctor to recognize the simple relationship between a weak acid, its anion base, and the hydrogen ion concentration."[4] The most important biologic acid-base buffer system includes carbonic acid (H_2CO_3), hydrogen ion (H^+), and bicarbonate ion (HCO_3^-). The concentration of H_2CO_3 is related to the partial pressure of carbon dioxide (pCO_2), the solubility of carbon dioxide in biologic fluids, and the combination of carbon dioxide with water to form H_2CO_3. The equations for these relationships lead to the usual form of the HHE as shown below.[6]

$$pH = 6.1 + \log\left(\frac{[HCO_3^-]}{0.03 * P_{CO_2}}\right) \qquad \text{(Eq 7)}$$

However, the question remained: how do biological systems respond to acute and chronic alterations in physiological pH? Henderson's formula provided physicians an accessible method to relate a patient's pH, bicarbonate level, and partial pressure of CO_2 but failed to provide information on the respiratory compensatory mechanisms of a patient. During the mid-20th century, two physicians, Horace W. Davenport and Robert W. Winters, would successfully explain these processes and change the foundation for our modern understanding of acid-base physiology.

Davenport diagrams

Horace Davenport remains a pivotal figure in acid-base physiology producing acid-base diagrams still used in modern medical education. Among his many accomplishments, Davenport "defined the gastric mucosal barrier, elucidated how various events would break the barrier and allow damage to the stomach, and identified the role of carbonic anhydrase in the parietal cells of the stomach. The work would pave the way for treatments such as H_2-receptor blockers and proton-pump inhibitors."[7] Davenport's book, *The ABC of Acid-Base Chemistry*, remains his lasting legacy and contribution in the medical profession.[6,8] In this book Davenport discusses the molecular mechanisms of pH change in the blood and the compensatory mechanisms involved.[6] The first section includes a detailed description of the physical chemistry, biochemistry, and fundamental equations involved in acid-base dynamics, including the HHE.[6] The second section contains a comprehensive description of the fundamental principles underlying Davenport diagrams, which graphically depict acute and chronic changes in pH, bicarbonate concentration, and dissolved arterial carbon dioxide.[6] As shown in Figure 1, the y-axis represents plasma bicarbonate concentration and x-axis represents pH.[6] The dashed line with negative slope represents the buffering capacity of blood achieved by changing pCO_2 via changes in alveolar ventilation, while the curved lines, known as isopleths, represent the HHE for different values of pCO_2 rewritten in the following form:

$$[HCO_3^-] = (0.03 * P_{CO_2})(10^{pH-6.1}) \qquad \text{(Eq 8)}$$

However, the blood buffer line is empirically derived due to the complex buffering activity among bicarbonate, protein, and miscellaneous organic buffers.[8,9] Using the Piiper method, the slope of the buffer (β) is determined through titrating non-bicarbonate buffers, such as lactic acid, against small changes in PCO_2 for a given bicarbonate concentration and analyzed using the equation below.[8,10]

$$\beta = \frac{\Delta[HCO_3^-]}{\Delta pH}$$

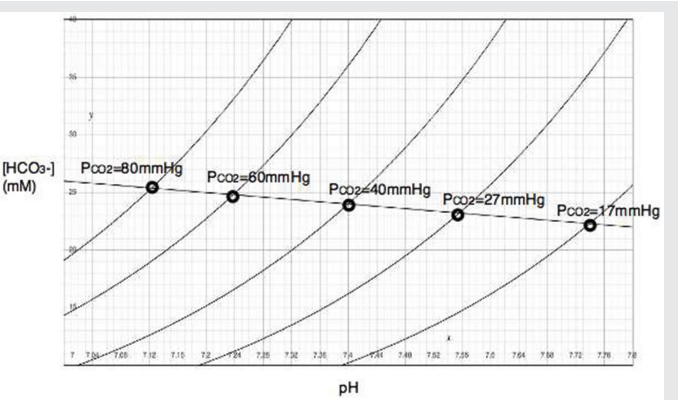

Figure 1. Davenport Diagram, https://en.wikipedia.org/wiki/Davenport_diagram

However, the addition of non-bicarbonate buffer titrates both the bicarbonate and protein buffers, limiting the overall accuracy of the method.[8] As such, any empirical determination of the buffer line will incorporate varying levels of uncertainty given the model's assumptions and methodology. There are no standard values for β. β can be computed from empiric values of bicarbonate concentration and pH observed in patients with acute respiratory acidosis or alkalosis. In our experience, an acute respiratory acidosis with pCO_2 of 50 torr is associated with a pH of about 7.32. Using Equation 8, one calculates a bicarbonate concentration of 24.894 for these conditions which is consistent with Figure 1. These data points combined with normal values of bicarbonate of 24 and pH of 7.40 yields a value for β of 11.175.

The intersections of the buffer line with the HHE curves yield the possible combinations of pH and bicarbonate concentration measured in the blood achievable by changes in alveolar ventilation.[6] Each black curve represents an isopleth for a single value of pCO_2. Each black curve represents the possible values of bicarbonate and pH for a single value of pCO_2, which models the effects of metabolic acidosis or alkalosis. The central circled point in Figure 1 is the normal value of pCO_2 of 40, pH of 7.40 and bicarbonate of 24. The dashed line through the other circled points represents the buffer line which shows the possible values of pH and bicarbonate achieved by changing pCO_2 through changes in minute ventilation. Movement along this dashed line represents respiratory acidosis (decreasing pH) or respiratory alkalosis (increasing pH).

With two independent axes of movement in the Davenport plane, any point in this plane representing any combination of pH and bicarbonate level can be represented by the vector sum along the two axes. The Davenport diagram becomes analogous to plotting points in a Cartesian plane with x and y axes.

Figure 2 represents a complex acid-base status combining acute metabolic acidosis followed by chronic compensation through respiratory alkalosis. An example would be diabetic ketoacidosis compensated by respiratory alkalosis. Point A is the starting point with normal pH, pCO_2, and bicarbonate level.

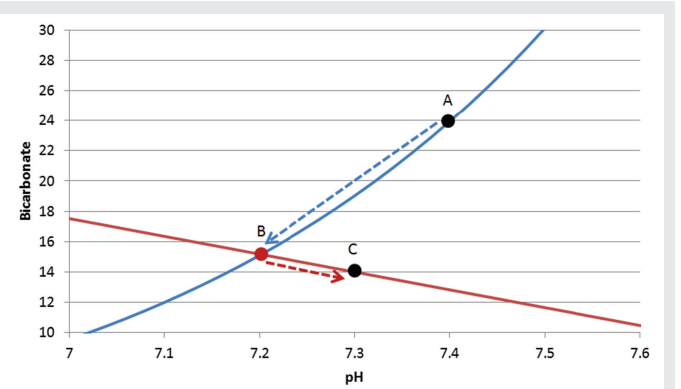

Figure 2. Acute metabolic acidosis with chronic respiratory compensation.

The blue curve is the Henderson-Hasselbach equation (Eq. 8) passing through point A. Point C is the final result. The brown line is the buffer line passing through point C. Point B is the intersection of the buffer line through Point C and the Henderson-Hasselbach equation through point A. The complex acid-base result of Point C can be seen to be the vector sum of an initial movement (blue dashed arrow) from point A to point B and the compensatory movement (red dashed arrow) from point B to point C. The blue dashed path represents the initial metabolic acidosis. The red dashed path represents the compensatory respiratory alkalosis.

Figure 3 is a second example of a complex acid-base status. The acute primary event is respiratory acidosis such as can occur in advanced chronic obstructive pulmonary disease. The chronic compensatory event is renal metabolic alkalosis achieved by the retention of bicarbonate. Point A is the starting point with normal values for pH, pCO_2, and bicarbonate. Point C is the final result of the complex acid-base status. The brown line is the buffer line through point A. The blue curve is the Henderson-Hasselbach equation through point C. The brown dashed line represents the initial respiratory acidosis. The dashed blue line represents the compensatory chronic metabolic alkalosis. Point C is the vector sum of the two processes.

As such, the Davenport diagram effectively describes the sequential respiratory-renal responses

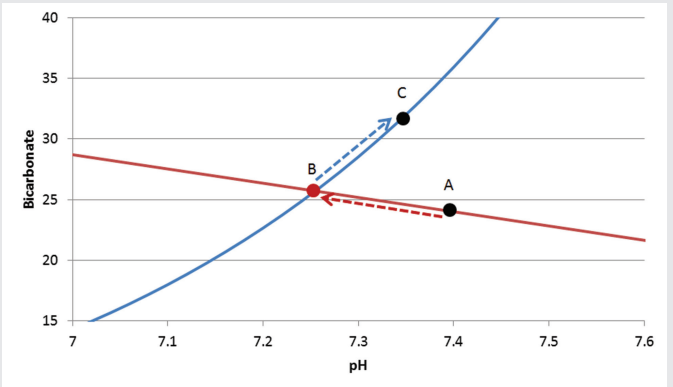

Figure 3. Acute respiratory acidosis with chronic renal compensation.

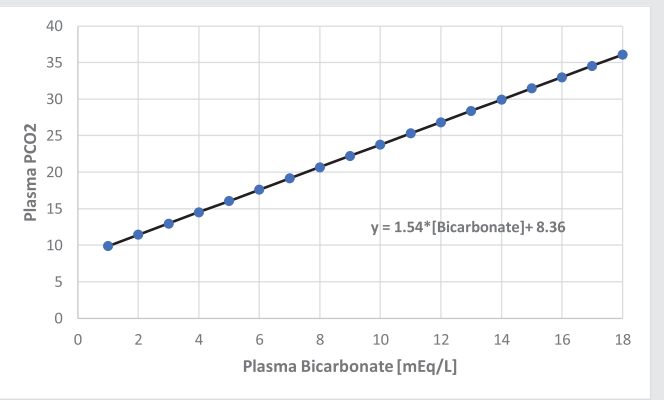

Figure 4. Relationship between plasma bicarbonate and plasma PCO_2.[11]

to several acid-base disturbances encountered in common clinical scenarios. However, the Davenport diagram describes only the theoretically possible compensations to primary acid-base disturbances without a means to monitor the real life limitations on compensation. While compensation for a primary acid-base disturbance can theoretically proceed all the way to pH 7.4, it does not always do so in clinical experience. The next breakthrough would come through the meticulous acid-base experiments conducted by Robert W. Winters.

Winters's formula

During the 1960s, Winters attempted to empirically determine a mathematical expression representing the limitation of respiratory compensation to uncomplicated metabolic acidosis.[11] Using 60 patients with diarrhea, diabetes, and renal disease, Winters measured the blood pH, plasma PCO_2, blood base excess, and plasma bicarbonate concentrations and performed a linear regression analysis of PCO_2 to various variables of acid-base balance equilibrium.[11] Among the variables measured, Winters was particularly interested in the relationship between plasma PCO_2 to plasma bicarbonate concentration as a model for uncompensated metabolic acidosis, as shown in Figure 4.

Using the regression line in Figure 4, a mathematical expression relating plasma PCO_2 to plasma bicarbonate concertation can be expressed as shown below:

$$PCO_2 = 1.5[HCO_3^-] + 8 \pm 2$$

The equation, known as Winters's formula, provides physicians a method for determining whether respiratory compensation to metabolic acid-base disturbance was complete or incomplete. Specifically, if the measured PCO_2 is greater or less than the PCO_2 predicted from Winters's formula, then either respiratory compensation is incomplete or there exists a second primary respiratory acid-base disturbance. Using this information, physicians may provide additional treatment or investigate other causes in a patient's acid-base disturbance, which would not have been considered otherwise. Previous attempts at formulating a mathematical expression of uncompensated metabolic acidosis were primarily retrospective, lacked specific inclusion criteria, and incorporated patients with minor metabolic acidosis.[11] Winters would later formulate a similar mathematical expression for chronic respiratory acidosis, as shown in Figure 5.

Thus, Winters's formula represented a significant advance in evaluating respiratory compensation to primary metabolic acid-base disorders and respond accordingly. However, as Winter's conceded, "The mechanisms responsible for initiating and sustaining this secondary respiratory adjustment

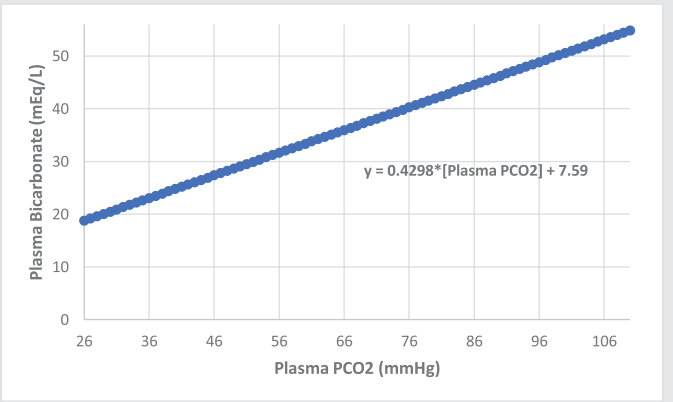

Figure 5. Relationships between plasma PCO2 and bicarbonate concentration under chronic respiratory acidosis.[12]

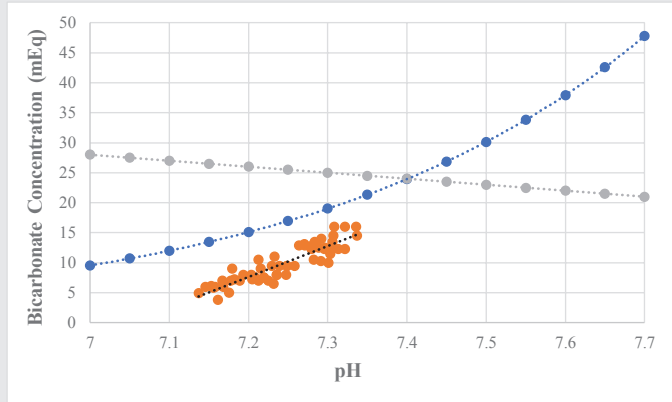

Figure 6. Davenport diagram and chronic metabolic acidosis.

in metabolic acidosis are incompletely understood."[11] Since Winters's work, extensive biochemical and physiological experiments have discovered a rich and elegant acid-base regulatory system Winters could never have imagined.

Winters's formula revisited

Through combining the Davenport diagram and Winters's chronic respiratory compensation values, a graphical representation of Winters's formula can be constructed, as shown in Figure 6.

In Figure 6, the blue curve shows the isopleth for pCO_2 of 40. This curve represents the possible combinations of bicarbonate and pH following primary metabolic acid-base disturbance. The grey line represents the buffer line through the normal value of pH = 7.4 and bicarbonate level of 24. Respiratory compensation to primary metabolic acid-base disturbance will follow a parallel line passing through an end point and intersecting the blue isopleth. Respiratory compensation can theoretically continue along this parallel buffer line all the way to pH = 7.4, but the orange points represent the practical limitation of respiratory compensation according to Winters's formula. The orange points are derived from Winters's data describing relationship between plasma pCO_2 and plasma bicarbonate concentration.[12] As such, Figure 6 represents the body's combined regulatory response to metabolic acidosis with respiratory compensation through the actions of the brain, lungs, and kidney. However, Winters was unable to elucidate the physiological changes producing two different mathematical expressions for metabolic and respiratory acidosis, as shown below:

Respiratory Compensation with Metabolic Acidosis

$$PCO_2 = 1.5[HCO_3^-] + 8$$

Chronic Respiratory Acidosis

$$[HCO_3^-] = 7.59 + 0.4298(PCO_2)$$

$$PCO_2 = 17.7 - 2.327[HCO_3^-]$$

Why is the respiratory compensation to metabolic acidosis limited to Winters's formula rather than completing a compensation to pH = 7.40? Unlike the HHE, Winters's formula is empiric rather than derived from first principles of physical chemistry. Although the mechanism for Winters's formula is not known at present, a number of plausible hypotheses can be advanced.

Acute respiratory acidosis is often the consequence of inability to increase alveolar ventilation in response to chemoreceptors regulating pH. In neuromuscular disease, the muscles cannot generate the mechanical force to adequately inflate the respiratory system. In musculoskeletal disease, the chest wall is too stiff for adequate inflation. In restrictive lung

disease, the lungs are too stiff for adequate inflation. In obstructive disease, the lungs cannot deflate during exhalation, leaving inadequate inspiratory capacity for subsequent breaths. These defects can all be considered as a reduction of open loop gain for the pH feedback control system. When open loop gain is reduced in feedback control systems, the tracking error between desired output and actual output necessarily increases. This tracking error is the cause of the primary respiratory acidosis. Patients with normal respiratory physiology do not possess infinite ability to compensate for metabolic acidosis. This finite ability also leads to limits in open loop gain which translate into measurable tracking errors for pH. These tracking errors could explain part of Winters's formula.

Although the primary determinant of alveolar ventilation in healthy subjects is pH, there are receptors for pCO_2 and pO_2 as well. Under normal conditions, these receptors are not fully suppressed and contribute some of the neural input driving alveolar ventilation. During metabolic acidosis, the pH receptors increase ventilatory drive leading to hyperventilation and the consequent decrease in pCO_2, an increase in pO_2, and a compensatory increase in pH. Compensatory hyperventilation decreases output from both the pCO_2 receptors and pO_2 receptors compared to the normal ventilatory state. The effect of compensatory hyperventilation, therefore, is to decrease ventilatory drive from the secondary pCO_2 and pO_2 receptors resulting in lower ventilator drive than would exist in the absence of these receptors.

Further experimental work is necessary to confirm the mechanism of Winters's formula. The obesity epidemic with the increasing incidence in chronic hypercapnic respiratory failure in patients with normal lungs may provide clinical material that increases understanding of the mechanism behind Winters's formula.

Conclusion

The HHE is derived from first principles of physical chemistry and describes the possible combinations of bicarbonate and pH due to metabolic acid-base disturbance. The buffer line is determined empirically and describes the possible values of bicarbonate and pH resulting from changes in alveolar ventilation starting from a given point on a Davenport diagram. Combined, these two methods can plot the possible compensatory responses to primary acid-base disturbances on a Davenport diagram. Winters's formula is an empiric tool indicating the practical limits to human compensatory responses to primary acid-base disturbances.

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