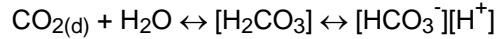


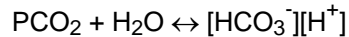
Acid-Base Lecture

Traditional Description of Acid-Base Chemistry

Acid-base physiology has traditionally been based on the CO₂ hydration reaction:



where CO_{2(d)} is dissolved carbon dioxide gas. Since the dissolved CO₂ gas can be expressed as a partial pressure, and the [H₂CO₃] concentration is both small and proportional to CO_{2(d)} the equation simplifies to:

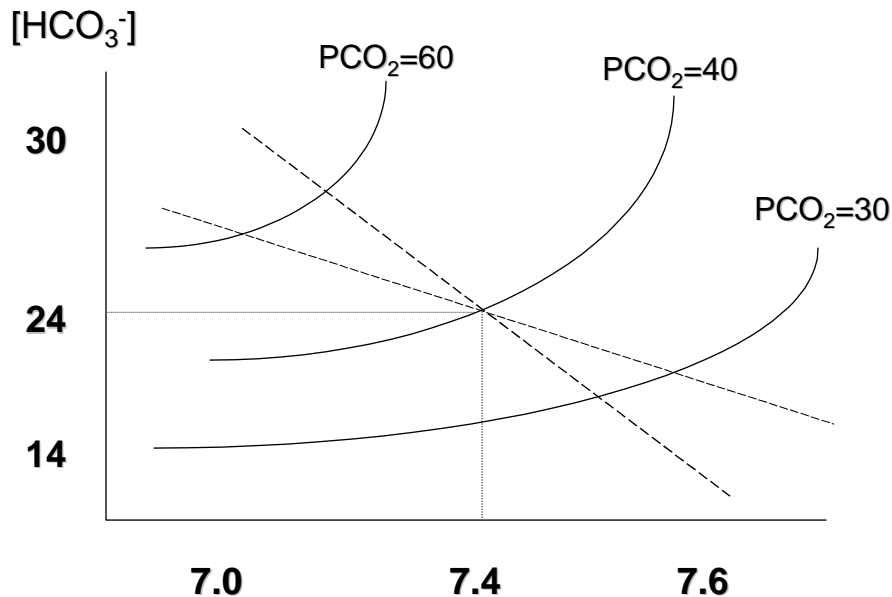


This is a chemical reaction, not a quantitative expression. In order to be useful the CO₂ hydration equation is converted to the well known Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK} + \log \frac{[\text{HCO}_3^-]}{\propto \text{PCO}_2}$$

where \propto has a value of 0.0301 and is the conversion coefficient expressing PCO₂ (normally in units of mmHg) to units of mMol/L, i.e. the same as [HCO₃⁻]. pK appears to be an equilibrium constant, but in reality is an empirically derived fudge factor that permits calculation of any one variable (usually [HCO₃⁻]) from measured pH and PCO₂. This is the equation that the blood gas machines utilize. The interaction between PCO₂, pH and [HCO₃⁻] can also be expressed graphically (Figure 1)

Figure 1



The curve lines represent PCO₂ isopleths, or lines of constant PCO₂. The straight line is called the respiratory buffer curve. The slope of the respiratory buffer curve increases as the hematocrit increases. Changes in the acid-base status along the respiratory buffer curve are called respiratory disturbances (alkalosis or acidosis), while changes along the PCO₂ isopleth are termed metabolic disturbances (alkalosis or acidosis). Any deviation of the acid-base status from either the buffer curve or the normal PCO₂ curve indicates:

- i) a metabolic compensation to a respiratory disturbance
- ii) a respiratory compensation to a metabolic disturbance
- iii) a combined respiratory and metabolic acid-base disturbance

Physiological mechanisms serve to minimize the change in pH. Respiratory compensation to metabolic acidosis is instigated within seconds to minutes, while metabolic compensation to respiratory acidosis occurs within minutes to hours. There are various formulas which describe the expected changes between pH, PCO₂ and [HCO₃⁻] with acute and chronic respiratory and metabolic acid-base disturbances. Table 1 below has been adapted from the Washington Manual and The ICU Book by P.L Marino (1991) :

<u>Type of Disturbance</u>	<u>Primary Change</u>	<u>Compensation</u>	<u>Expected Change</u>
Metabolic Acidosis	[HCO ₃ ⁻] decreases	PCO ₂ decreases	- PCO ₂ = 1.5[HCO ₃ ⁻] + 8 ± 2 - ΔPCO ₂ = 1-1.3(Δ[HCO ₃ ⁻])
Metabolic Alkalosis	[HCO ₃ ⁻] increases	PCO ₂ increases	- PCO ₂ : variable increase - PCO ₂ = 0.9[HCO ₃ ⁻] + 9 - PCO ₂ increases 0.6 mmHg/ mEq/L increase in [HCO ₃ ⁻]
Respiratory Acidosis	PCO ₂ increases	[HCO ₃ ⁻] increases	<u>Acute:</u> - [HCO ₃ ⁻] increases 1mEq/L for every 10 mmHg increase in PCO ₂ - ΔpH = 0.008ΔPCO ₂ <u>Chronic:</u> - [HCO ₃ ⁻] increases 3.5 mEq/L for every 10 mmHg increase in PCO ₂ - ΔpH = 0.003ΔPCO ₂
Respiratory Alkalosis	PCO ₂ decreases	[HCO ₃ ⁻] decreases	<u>Acute:</u> - [HCO ₃ ⁻] falls 2 mEq/L for each 10 mmHg fall in PCO ₂ - ΔpH = 0.008ΔPCO ₂ <u>Chronic:</u> - [HCO ₃ ⁻] falls 5 mEq/L for each 10 mmHg fall in PCO ₂ - ΔpH = 0.017ΔPCO ₂

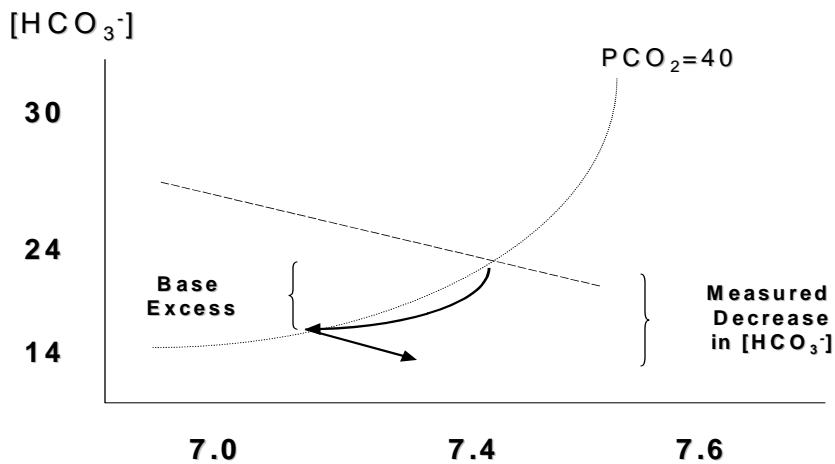
Concept of Base Excess/Base Deficit (Negative Base Excess)

Inspection of Figure 2 shows that $[\text{HCO}_3^-]$ changes with both respiratory and metabolic acid-base disturbances. The concept of base excess was developed to determine how much of the change in $[\text{HCO}_3^-]$ was due to metabolic disturbance alone. This is important because it is a reflection of the amount of fixed acid (or base) that is being generated (lactate is the most common fixed acid). The base excess is calculated using the relationship between hematocrit/hemoglobin and the buffer line:

$$\text{BE} = (1 - 0.014\text{Hgb}) (\text{HCO}_3 - 24 + (1.43\text{Hgb} + 7.7) (\text{pH} - 7.4))$$

Knowing this relationship it is possible to calculate what the $[\text{HCO}_3^-]$ would be during a metabolic disturbance (alkalosis or acidosis) if there were no respiratory compensation, i.e. PCO_2 was 40 mmHg. The concept of base excess is depicted below:

Figure 2



Acid-Base and Temperature

Water exists in a dissociated state $[\text{H}_2\text{O}] K_w = [\text{H}^+] \times [\text{OH}^-]$. The affect of temperature is to increase the dissociation constant (K_w), there is more energy in the bonds between H^+ and OH^- in H_2O . The greater the value of K_w , the more protons and hydroxyl ions exist.

Since pH is the negative log of the hydrogen concentration, the pH of water increases as the temperature decreases, and vice versa. We are accustomed to thinking that 'neutral pH' is 7.0; but this is only true at 25°C. At 0°C water is 7.425 (but this pH is still neutral) and at 37°C it is 6.796 (but still neutral pH). The pH will change with temperature, but not the acidity, i.e. the pH of neutrality changes with temperature, $[\text{H}^+] = [\text{OH}^-]$. The change in pH of water with temperature = -0.017 pH units/1°C.

Since plasma is mostly water, the same (similar) chemistry applies. At 37°C, neutral pH is 6.796, our pH is 7.4 and therefore we are alkalotic. During cardiopulmonary bypass, the body is cooled to about 30°C. At this temperature the pH of neutrality is increased from 6.796 to 6.847. The pH of blood will also increase, but by how much? Certainly the water component of the body will be affected in exactly the same way, as will all chemical species with dissociation constants close to pH 7. The affect of temperature on dissociation constants that are far from 'neutrality' will not be greatly affected. The shape of proteins is extremely important to their function, and the shape of

proteins is highly dependent upon the balance of charges on the amino acids, and the environment in which the proteins exist. Of the ionic species on amino acids, the most important is the imidazole group on histidine. This moiety has almost the exact same sensitivity to temperature as water, $\Delta pK/\Delta T = -0.016$ pK units/ $^{\circ}C$. Thus, while changes in temperature will affect pH of water, the ionization state of proteins maintains the same relative to this pH. Maintaining the same degree of 'alkalinity' to the aqueous environment allows proteins to maintain their structure, and thus function, regardless of the temperature. This is the approach to acid-base balance taken by cold blooded animals (poikilotherms) and is termed alpha stat. The alpha-stat hypothesis contends that histidine imidazole ionization state is a primary determinant of the charge state and the pH-dependent functions of most of the body's proteins. With alpha stat management, changing temperature does not alter histidine ionization and, hence, pH of neutrality, protein charge state, structure, and function are better preserved.

The physiology is not quite this straight forward because of a second affect of temperature; the solubility of gases (CO_2) increases with decreasing temperature, thus lowering the PCO_2 and increasing HCO_3^- (the total amount of carbon dioxide stays constant). For poikilotherms it is quite normal for them to exist in a state of 'relative respiratory alkalosis' because this maintains the proper ionization of histidine. Applying the alpha stat theory to cardiopulmonary bypass (or deliberate hypothermia) means to measure the blood gases at $37^{\circ}C$ and make any adjustments necessary to maintain pH of 7.4 and PCO_2 of 40 mmHg AT $37^{\circ}C$. The actual pH and PCO_2 (measured at $30^{\circ}C$) would be 7.5 and 29 mmHg respectively.

The other approach to temperature and acid-base is illustrated by hibernating animals, they hypoventilate and allow their PCO_2 to increase. This is termed pH-stat and means that the goal is to maintain pH at 7.4 and PCO_2 of 40 mmHg AT THE TEMPERATURE OF THE BODY, i.e. $30^{\circ}C$ in our example. In order to accomplish this it is necessary to add CO_2 to the inhaled gas. This would produce a relative hypercarbia and acidemia compared to alpha-stat.

Temperature	Measured and Reported at $37^{\circ}C$				Corrected to In Vivo			
	pH		PCO_2		pH		PCO_2	
in vivo temp	alpha stat	pH stat	alpha stat	pH stat	alpha stat	pH stat	alpha stat	pH stat
37	7.4	7.4	40	40	7.4	7.4	40	40
33	7.4	7.34	40	47	7.44	7.4	35	40
30	7.4	7.3	40	54	7.5	7.4	29	40
27	7.4	7.26	40	62	7.55	7.4	26	40
23	7.4	7.21	40	74	7.6	7.4	22	40
20	7.4	7.18	40	84	7.65	7.4	19	40

From the table it can be seen that at an in vivo temperature of $30^{\circ}C$ with alpha stat the pH would be 7.4 at $37^{\circ}C$ and the PCO_2 would be 40 mmHg. Either correcting for temperature, or lowering the temperature of the electrodes, the actual pH and PCO_2 would be 7.5 and 29 mmHg respectively at $30^{\circ}C$. Conversely using pH stat at $30^{\circ}C$ the pH and PCO_2 would be adjusted to 7.3 and 54 mmHg (measured at $37^{\circ}C$), but would be 7.4 and 40 mmHg in the body at $30^{\circ}C$.

The obvious question is which approach is appropriate for humans, considering they are neither poikilotherms nor hibernate. A significant amount of work has been done to answer the question.

Cardiac

Dog model and human studies suggest worsened VF threshold when pH stat used at $25^{\circ}C$, and improved cardiac stability with alpha stat

Other clinical studies show no difference in cardiac outcome with respect to shocks, IABP, MI, inotropes during cardiac surgery.

CNS

Cerebral Blood Flow response to PCO_2 is preserved during cooling. Patients treated via pH stat tend to have greater CBF and maybe loss of autoregulation. Conversely autoregulation and matching between cerebral metabolic need and oxygen delivery is usually seen to be preserved with alpha stat.

No difference in neurological outcome have been seen with either approach.

The Bottom Line – there is no overwhelming evidence to support one approach over another, but the science supports alphastat.

Diagnosis of Acid-Base Disturbance

The approach to most acid-base disturbances is relatively straightforward. The steps are:

What type of acid-base disturbance, acidosis or alkalosis ?

Low pH	acidosis
Is PCO_2 low or high	- high PCO_2 with low pH is a primary respiratory acidosis - low PCO_2 with low pH is a metabolic acidosis being compensated by hyperventilation
High pH	alkalosis
Is PCO_2 low or high	- low PCO_2 is a primary respiratory alkalosis - high PCO_2 is a primary metabolic alkalosis with compensatory hypoventilation

Using the calculations from Table 1 it is possible to assess if the changes in PCO_2 , $[\text{HCO}_3^-]$ and pH are all appropriate, or is there a combined respiratory and metabolic acid-base disturbance.

Metabolic Alkalosis

A metabolic alkalosis is characterized by a high $[\text{HCO}_3^-]$ compensated by increased PCO_2 secondary to reduced ventilation. This is somewhat similar to chronic CO_2 retention in the COPD patient. However, the major difference is that pH will be alkalotic in the former, but acidotic in the later. The mechanism(s) responsible for causing and maintaining a metabolic alkalosis are complicated but often involve loss of gastric acid from vomiting or overzealous NG suction, loop diuretics. Maintenance of the alkalotic state is often associated with hypovolemia and hypokalemia. Decreased ECV turns on the renin/angiotensin/aldosterone system resulting in increased sodium reabsorption and potassium secretion.

Metabolic Alkalosis

Comments

1) Loss of gastric fluid and hypovolemia	Rx with NaCl replacement
2) Hypokalemia + loss of gastric fluid and hypovolemia	K replacement plus volume replacement
3) Increased distal salt delivery (loop diuretics)	
4) Mineralocorticoid excess	normal urine $[\text{Cl}^-]$, ECV
5) Overly aggressive $[\text{HCO}_3^-]$ therapy for metabolic acidosis	see below
6) Hypo-proteinemia	see below

Metabolic alkalosis, while potentially a problem with respect to hypoventilation and cardiac dysrhythmias, are usually well tolerated and correction of volume, sodium, chloride and potassium should occur over several days.

Metabolic Acidosis

Diagnosis of a metabolic acidosis can be facilitated by calculation of the anion gap:

$$[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{HCO}_3^-] = \text{anion gap}$$

The anion gap is equivalent to the negative charge on plasma proteins and phosphate. The law of electrical neutrality states that the anion gap **MUST** equal the electrical charge on the other side of the equation, i.e.:

$$[\text{Protein}^-] = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$$

If there is a discrepancy, i.e. the anion gap > than the other side of the equation, or the anion gap > 14-16 mEq/L then suspect the presence of a fixed acid:

$$[\text{Protein}^-] + [\text{Lactate}] = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$$

Other causes of a wide gap acidosis include:

- 1) Lactacidosis (either increased production or decreased metabolism)
- 2) Ketoacidosis
- 3) Renal failure - Uremia
- 4) Toxins - salicylates (this usually produces a respiratory alkalosis first)
 - methanol (produces formic acid, Rx with ethanol)
 - ethylene glycol (metabolized to glycolic and oxalic acid, Rx with ethanol)
 - paraldehyde (Rx with volume and bicarbonate)

If the anion gap is small then consider the following as the potential problem:

Low $[\text{K}^+]$

- 1) Diarrhea
- 2) Pancreatic, biliary fistula
- 3) Uretersigmoidostomy
- 4) Renal tubular acidosis
- 5) Mild renal insufficiency
- 6) Volume infusion with NaCl

Normal-High $[\text{K}^+]$

- 1) Hyperalimentation
- 2) Posthypocapnia
- 3) Rapid hydration (dilutional acidosis)
- 4) Hypoaldosteronism

A major difference between wide gap or narrow gap acidosis is that narrow gap etiologies are more benign and seem to be better tolerated. They do not indicate systemic poisoning of cellular metabolism.

Approach and Treatment

A severe metabolic acidosis must be treated quickly in order to minimize damage to metabolism (enzymes do not work in abnormal acidity) and cardiovascular stability (increased dysrhythmias and decreased contractility) but ultimate therapy is directed at the cause. Usually a pH less than 7.35 requires heightened awareness that there is a problem and appropriate steps need to be instigated. Respiratory acidosis requires increased alveolar ventilation through manipulation of airway or mechanical support. Respiratory acidosis is usually accompanied by hypoxemia (asthmatic, foreign body, airway trauma, COPD) which is obviously your first concern. Metabolic

acidosis is treated initially with maximizing tissue perfusion so as to remove acid through metabolism, removing acid through dialysis and/or increasing alveolar ventilation in order to correct the pH. The order of treatment varies with the underlying cause. Bicarbonate therapy is usually not instigated until the $[\text{HCO}_3^-]$ is much less than 18 mMol/L. The goal of bicarbonate therapy is to increase $[\text{HCO}_3^-]$ only to 18 mMol/L. The formula for bicarbonate replacement is:

$$0.5 \times \text{body weight} \times \text{desired change in bicarbonate.}$$

If bicarbonate therapy increases $[\text{HCO}_3^-]$ much more than 18 mMol/L you run the risk of causing either metabolic alkalosis when the fixed acid is removed through metabolism or dialysis and/or causing volume overload from all the sodium you gave with the $[\text{HCO}_3^-]$. As stated above however, all of this is going on with simultaneous investigation of cause and definitive treatment. **Remember, acid-base disturbances are not diseases, but symptoms of disease.** The type of acid-base disturbance may help with the ultimate diagnosis, i.e. respiratory, wide gap, narrow gap, acute vs chronic.

Now for Something Completely Different

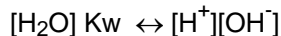
The above is a summary of acid-base chemistry/physiology as presented in most text books. While it may appear straight forward, a closer look reveals a major problem. All of the above is based on the CO₂ hydration reaction. This NON-QUANTITATIVE chemical description was re-arranged into a mathematical expression and was then re-displayed in graphical form on which disturbances in acid-base physiology could be illustrated. Any mathematical description is predictive, i.e. if you know one side of the equation you can predict the outcome. The term 'quantitative description' means a mathematical description that is based on cause and effect rather than an empiric relationship. Both may predict 'Y' from a known value of 'X', but only a 'quantitative' expression tells you what the underlying mechanism is. To illustrate the fact that the CO₂ hydration reaction, and by extension the Henderson-Hasselbalch equation, is not completely quantitative you only have to equilibrate water with CO₂ at 40 mmHg (equal to about 5%) and measure the pH and [HCO₃⁻]. If they come out even close to physiologically normal numbers you have confidence that the CO₂ hydration reaction is a complete, quantitative description of acid-base chemistry in physiological systems. If you measure pH and [HCO₃⁻] that differ widely from physiologically normal numbers it suggests either the CO₂ equation is wrong (not likely) or it is an incomplete description of the system. In fact, when water is equilibrated to PCO₂ of 40 mmHg, the pH is around 3-4 and [HCO₃⁻] is less than 1 mMol/L. The obvious answer is that there are 'buffers' in plasma that are not found in the CO₂/H₂O mixture. While true, the extent of the discrepancy between predicted and observed results suggests that the effect of these buffers is both powerful and completely unexplained in a 'quantitative' manner.

Thus we have a need to develop equations that 'describe' normal acid-base chemistry. Once we know how a physiologically normal pH and [HCO₃⁻] is obtained in plasma at a PCO₂ of 40 mmHg we will then have a much better set of tools to figure out what is going wrong with acid-base physiology in disease processes.

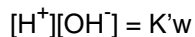
Modern Quantitative Acid-Base Chemistry

The physico-chemical approach to acid-base chemistry was first re-discovered by Dr. Peter Stewart in the early 1980's (1978; 1983) and but is only now beginning to make headway into the medical literature (references 1-12).

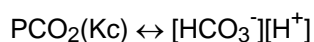
The goal is to develop all the equations that are pertinent to acid-base chemistry in plasma, not just in water. Since plasma is mostly water however, the first equation should be the dissociation of water:



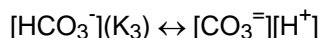
Since the concentration of [H₂O] is so large it can be viewed as a constant and the equation simplifies to:



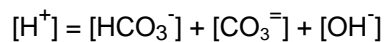
where K_w is [H₂O] + K_w. The second equation is the CO₂ hydration reaction already discussed:



Bicarbonate dissociates a second time to carbonate:



At this point it is useful to examine these equations from the point of view of assessing independent and dependent variables. The definition of an independent variable is that it is determined from outside the system, has an influence on the system, but is not influenced by the system. The system in this case is plasma (it does not matter if it is in a test tube or in the blood). Looking at CO₂ we know that PCO₂ is a function of alveolar ventilation and metabolic rate. The amount of CO₂ in plasma is not determined by the concentration [HCO₃⁻] or [H⁺]. However, the concentration of [H⁺] and [HCO₃⁻] (and by extension [CO₃⁼] and [OH⁻]) is determined by PCO₂. Thus, PCO₂ satisfies the definition of being an independent variable and [H⁺], [OH⁻], [HCO₃⁻] and [CO₃⁼] are all dependent variables, they are all determined by the prevailing PCO₂ which is dependent upon alveolar ventilation. This leaves us with 4 unknowns but only three equations so the system cannot be solved as such. This dilemma has a solution in that there is a fourth equation - that of electrical neutrality (remember the anion gap). The fact that all positive and negative charges must balance is a rule of physics, i.e. a gold standard. Thus:



We now have four equations and four unknowns (dependent variables). Inspection illustrates how dissolving CO₂ in water can never generate much [HCO₃⁻] because it can never be greater in concentration than [H⁺] and still obey the law of electrical neutrality. Our experiment of equilibrating water to a PCO₂ of 40 mmHg resulted in a pH of 3, not 7.4. At a pH of 3.0, [H⁺] = 1 mEq/L which would also be the theoretical maximum concentration of [HCO₃⁻], assuming [CO₃⁼] and [OH⁻] were 0 (which is impossible).

One of the big differences between a system consisting of water and CO₂ vs. plasma is the presence of strong electrolytes in plasma. Strong electrolytes (or strong ions) are defined as those which completely dissociate in water, i.e. [Na⁺], [K⁺], [Cl⁻], [Ca²⁺], [Mg²⁺] as well as strong organic acids such as [lactate], [formate] or [keto acids]. Since these strong ions have a charge associated with them, this charge must be accounted for in the last equation of electrical neutrality. It is not the strong ions specifically which are important, it is the charge difference between them. Thus:

[Na⁺] + [K⁺] + [divalent cations] - [Cl⁻] - [strong organic acids] = the **strong ion difference** or [SID]

Simplifying by ignoring the small contribution of divalent cations and usually low concentration of strong organic acids:

$$\begin{aligned} [Na^+] &+ [K^+] - [Cl^-] &= [SID] \\ 140 \text{ mEq/L} &+ 4 \text{ mEq/L} - 100 \text{ mEq/L} &= 44 \text{ mEq/L} \end{aligned}$$

Thus, [SID] represents 44 mEq/L of positive charge that **must** be balanced by negative anions. Summarizing and including [SID] in the equation of electrical neutrality:

$$\begin{aligned} [H^+] [OH^-] &= K'w \\ PCO_2 (Kc) &= [HCO_3^-][H^+] \\ [HCO_3^-](K_3) &= [CO_3^{=}] [H^+] \\ [SID] + [H^+] - [HCO_3^-] - [CO_3^{=}] - [OH^-] &= 0 \end{aligned}$$

Inspection reveals that [SID] is also an independent variable. [SID] will have an influence on the system in that the concentration of [H⁺], [HCO₃⁻], [CO₃⁼] and [OH⁻] will all re-adjust according to

both their individual equilibrium constants (K'_w , K_c , K_3) and to the satisfaction of the **law of electrical neutrality**. However, none of these variables will influence the concentration of strong ions and therefore the concentration of [SID]. Thus we have four equations and four unknowns (dependent variables), two independent variables (PCO_2 , and [SID]) and three parameters (K'_w , K_c , K_3). These equations can be solved for any of the four dependent variables. Solving for $[H^+]$ by expressing all the remaining three dependent variables only in terms of independent variables and parameters:

$$\begin{aligned} [OH^-] &= K'_w/[H^+] \\ [HCO_3^-] &= K_c \times PCO_2/[H^+] \\ [CO_3^{2-}] &= [HCO_3^-](K_3)/[H^+] \\ &= /[H^+] \\ &= K_3 \times K_c \times PCO_2/[H^+]^2 \end{aligned}$$

and substituting for each dependent variable into the equation for electrical neutrality:

$$[SID] + [H^+] - K'_w/[H^+] - K_c \times PCO_2/[H^+] - K_3 \times K_c \times PCO_2/[H^+]^2 = 0$$

multiplying through by $[H^+]^2$ and rearranging terms gives:

$$[H^+]^3 + [SID][H^+]^2 - (K_c \times PCO_2 + K'_w)[H^+] - K_3 \times K_c \times PCO_2 = 0$$

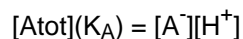
This is a third order polynomial equation of the form:

$$AX^3 + BX^2 + CX + D = 0$$

for which we know all the values for A, B, C and D and can thus solve for X (in this case $X = [H^+]$). This equation can be solved by a computer program that keeps trying different concentrations of $[H^+]$ until the answer is zero. This is called an iterative approach. Substituting a value of 42 mEq/L for [SID] and 40 mmHg for PCO_2 and using values for the dissociation constants found in text books allows the equation to be solved for $[H^+]$. Doing so predicts an $[H^+] = 2.35 \times 10^{-8}$ Eq/L or a pH of 7.63. This value of pH or $[H^+]$ (plus a PCO_2 of 40 mmHg) can then be substituted into the Henderson-Hasselbalch equation to predict $[HCO_3^-]$ of 43.9 mEq/L.

While this amount of chemistry shows an improvement in that the predicted pH and $[HCO_3^-]$ are in closer agreement to physiologically normal numbers than just looking at CO_2 /water, it is not close enough. Obviously pH and $[HCO_3^-]$ values are too high, too alkalotic. An acid must be added.

Recalling the concept of anion gap from the 'traditional approach to acid-base' suggests that plasma proteins are acids. The anion gap is the negative charge associated with proteins, i.e. proteins exist as both undissociated [ProteinH] and dissociated protein $[Protein^-] + [H^+]$. The dissociation constant for proteins is somewhat less than physiological pH (= 6.7). Therefore while most of the protein will exist as dissociated proteinate, some will exist in the undissociated form. Thus, proteins are termed weak acids because they do not completely dissociate in water (in contrast to strong acids which are completely dissociated). Phosphates are also weak acids. The influence of both proteins and phosphates can be combined and termed total weak acid concentration ([Atot]). Thus the dissociation reaction for [Atot] is:



In addition to the dissociation reaction for weak acids, the total concentration of weak acids will always equal the sum of the dissociated and undissociated species:

$$[\text{Atot}] = [\text{A}^-] + [\text{AH}]$$

This is known as the conservation of mass. Both equations must be included in the physico-chemical description:

$$\begin{aligned} [\text{H}^+] [\text{OH}^-] &= K_w \\ \text{PCO}_2 (K_c) &= [\text{HCO}_3^-][\text{H}^+] \\ [\text{HCO}_3^-](K_3) &= [\text{CO}_3^{2-}][\text{H}^+] \\ [\text{Atot}](K_A) &= [\text{A}^-][\text{H}^+] \\ [\text{Atot}] &= [\text{A}^-] + [\text{AH}] \end{aligned}$$

$$[\text{SID}] + [\text{H}^+] - [\text{A}^-] - [\text{HCO}_3^-] - [\text{CO}_3^{2-}] - [\text{OH}^-] = 0$$

Inspection reveals that [Atot] is also an independent variable. The total weak acid concentration is not influenced by the concentration of dissociated or undissociated weak acids, or any of the other dependent variables. The total weak acid concentration is a function of metabolism and volume of distribution. Think of adding 80 g of protein to a liter of water. You will have a concentration of 80 g/L no matter how much dissociates or what the [H⁺] is.

We now have six equations with six unknowns, which can be solved as above and result in a 4th order polynomial. Substituting normal values for PCO₂, [SID] and [Atot] and solving the solution for [H⁺] a [H⁺] concentration of 4.0 x 10⁻⁸ Eq/L or pH = 7.397 is predicted. Substituting the predicted pH into the Henderson Hasselbalch equation gives a predicted [HCO₃⁻] of 25.8 mMol/L. Thus the 4th order polynomial solution to these 6 equations correctly predicts physiological values for pH and [HCO₃⁻]. **These six equations are all necessary to completely describe normal acid-base chemistry in plasma:**

$$[\text{H}^+] \text{ and } [\text{HCO}_3^-] = f([\text{SID}], \text{PCO}_2, [\text{Atot}])$$

Moving on to physiology we can state:

- i) the prevailing [H⁺] and [HCO₃⁻] in plasma, in both health and disease, is determined by three independent variables - PCO₂, [Atot] and [SID]
- ii) a change in [H⁺] and [HCO₃⁻] can only occur if there has been a change in one or more of the three independent variables
- iii) adding or subtracting [H⁺] or [HCO₃⁻] (via either gut or kidneys) is totally irrelevant to the concentration of [H⁺] or [HCO₃⁻], so do not bother looking for where [H⁺] or [HCO₃⁻] are being lost or added to the body, think about how the three independent variables have changed.
- iv) change in [H⁺] or [HCO₃⁻] cannot influence each other

Bottom Line - What You Have to Know

While all this may seem overwhelming don't worry. It is not important that you be able to derive and solve 6 simultaneous equations. It is only important that you know that ANY acid-base disturbance is caused by a change in SID, PCO₂ and/or weak acids (plasma proteins). Here is how it works at 0300 hours:

- 1) low pH for any reason is bad because it can cause cardiac irritation
- 2) hypercapnia with low pH is bad because it means high dead space and can cause CNS changes - these are airway problems – asthma, pulmonary edema, infection, malignancy, foreign bodies, etc. Don't forget that some COPDers' walk around with PCO₂ levels over 60 mmHg (there pH is almost normal because their SID is increased – usually low Cl). Don't over ventilate and make them alkalotic – it will reduce their drive to breathe.
- 3) low pH associated with low PCO₂ is either a metabolic (lactate) problem or an electrolyte problem (low Na/high Cl). Treatment depends on the situation – shock, focal ischemia, renal failure, GI loss, iatrogenic. Usually giving bicarb will just increase the Na level. While this in itself will increase SID and therefore improve pH somewhat it may also cause other problems. The body does not like hyponatremia. A lactacidosis means that there is lactic acid in the plasma, but more importantly it means there is lactic acid IN THE CELLS. This is what is important because it is the cells that are alive, not plasma, and giving bicarb is of questionable benefit to cells. It is probably more useful to support ventilation and drive PCO₂ down to ~30 mmHg, provide volume and optimize cardiac function than to give bicarb.
- 4) Calculations are easy at 3 in the morning
 - a. Get the electrolytes and calculate SID (Na + K – Cl)
 - b. Get lactate if you think it will be elevated and calculate SID (Na + K – Cl – Lact)
 - c. Measure PCO₂ – the goal is to either correct PCO₂ for any respiratory/alveolar ventilation problems, or to titrate PCO₂ to normalize pH
 - d. See if you can get some idea of Total protein – either measure it directly, or from albumin (low albumin means low Prot-, it is the primary weak acid)
 - e. If you can get the Total Protein then calculate Prot- (the anion gap) from:
$$\text{Prot- (mEq/L)} = \text{Total Protein (g/L)} \times 0.23$$
 - f. Estimate electrical neutrality from:
$$\text{SID} - \text{HCO}_3 - \text{Prot-} \sim 0 \pm 5 \text{ mEq/L}$$
 - g. If electrical neutrality is achieved then you have a diagnosis of the acid-base disturbance, this will guide treatment of the acid-base disturbance, and facilitate diagnosing the primary pathology
 - h. If electrical neutrality is not approximated then you are either missing something (phosphate, etc.) or there is a measurement error. Remember that Na and Cl levels are only accurate to ~2%. A Na of 140 could be anywhere between 143 and 137, a Cl of 100 could be 102 to 98. There is lots of room for error here. Check results again if things are serious, look for average value if numerous measurements are obtained (the ICU routinely measures electrolytes several times/day)

Clinical Examples

Case 1

65 yo male presents to ED with 8 hours of progressive Rt flank pain. He is febrile with a blood pressure of 90/60 and a heart rate of 120 bts/min.

Arterial blood gas reveals:

$$\text{pH} = 7.259$$

$$\text{PCO}_2 = 35$$

$$[\text{HCO}_3^-] = 16.4$$

Electrolytes:

$$[\text{Na}^+] = 138$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 100$$

Traditional approach tells you that this is a septic shock with significant metabolic acidosis and some degree of compensation through hyperventilation. The anion gap is $138 + 4 - 100 - 16.4 = 25.6$. Since this is a wide gap acidosis you look for more acid. The history suggests renal infection and sepsis.

Lactate comes back at 8 mEq/L

It is possible that there maybe a respiratory component to the acidosis so you look at the formulas for pH/PCO₂/[HCO₃⁻]

$$\begin{aligned}\text{Expected PCO}_2 &= 1.5[\text{HCO}_3^-] + 8 \\ &= 1.5(16) + 8 \\ &= 32\end{aligned}$$

alternatively

$$\begin{aligned}\Delta\text{PCO}_2 &= 1.2(\Delta[\text{HCO}_3^-]) \\ \Delta\text{PCO}_2 &= 1.2 (24-16) = 9.6 \\ \text{PCO}_2 \text{ should be } &40 - 9.6 = 30.4 \text{ mmHg}\end{aligned}$$

Since the PCO₂ is higher than predicted at 35 mmHg, this is a combined metabolic and respiratory acidosis, possibly due to fatigue and/or COPD. Treatment involves providing oxygen, fluid/inotropes, invasive monitoring in the ICU, antibiotics and investigation for stones or obstruction that could be relieved. Would you give bicarbonate ?

Case 2

Same history as above, except that the patient looks a little wasted from poor nutrition.

Electrolytes come back as above:

$$[\text{Na}^+] = 138$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 100$$

However, the blood gas does not appear to be quite as bad:

$$\text{pH} = 7.377$$

$$\text{PCO}_2 = 35$$

$$[\text{HCO}_3^-] = 21.5$$

$$\text{Anion gap} = 138 + 4 - 100 - 21.5 = 20.5$$

The predicted PCO_2 is:

$$\begin{aligned}\text{PCO}_2 &= 1.5([\text{HCO}_3^-]) + 8 \\ &= 1.5(21) + 8 = 39\end{aligned}$$

or

$$\Delta\text{PCO}_2 = 1.2 (\Delta[\text{HCO}_3^-]) = 1.2 \times (24 - 21) = 37$$

Thus, the PCO_2 is, if anything a little lower than expected suggesting the possibility of a respiratory alkalosis, due to pain, anxiety? Would you still have the same concerns about the severity of the metabolic derangement and possible need for ICU, monitoring and intubation. Surprisingly the lactate still comes back as 8 mEq/L !! There is something different about this presentation than the first! Is this patient just as sick?

Case 3

Same history as above, except the patient history reveals mild congestive heart failure and proteinuria.

Electrolytes:

$$[\text{Na}^+] = 138$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 100$$

Arterial blood gas is:

$$\text{pH} = 7.419$$

$$\text{PCO}_2 = 35$$

$$[\text{HCO}_3^-] = 23.7$$

$$\text{Anion gap} = 138 + 4 - 100 - 23.7 = 18$$

The slightly elevated pH and lower PCO₂ suggests a primary respiratory alkalosis. The history suggests this is a relatively acute event. Therefore, the predicted pH would be:

$$\Delta\text{pH} = 0.008\Delta\text{PCO}_2$$

$$= 0.008 (40-35)$$

$$= 0.04$$

$$\text{pH} = 7.4 + 0.04 = 7.44$$

and the predicted [HCO₃⁻] is:

$$\Delta[\text{HCO}_3^-] = 2 \text{ mMol/L}/10 \text{ mmHg PCO}_2$$

$$= 1 \text{ mMol/L}$$

$$[\text{HCO}_3^-] = 24 - 1 = 23 \text{ mMol/L}$$

Would you suspect a significant metabolic acidosis on this information? Surprisingly the lactate still comes back as 8 mEq/L!! What is responsible for the differences between these three cases?

Investigation based on physico-chemical principles

Case 1

Same history as above.

$$[\text{Na}^+] = 138$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 100$$

$$[\text{SID}] = 42$$

$$\text{pH} = 7.259$$

$$\text{PCO}_2 = 35$$

$$[\text{HCO}_3^-] = 16.4$$

$$\text{Tprot} = 80 \text{ g/L}$$

To estimate $[\text{A}^-]$ (i.e. the anion gap) multiply $[\text{Tprot}]$ g/L by 0.23. Thus, a $[\text{Tprot}]$ of 80 g/L is equivalent to 18 mEq/L of $[\text{A}^-]$. Remember $[\text{A}^-]$ is equivalent to the negative charge on protein and is supposed to equal the anion gap. To be more accurate (only for the keeners):

$$[\text{A}^-] = \text{anion gap} = \frac{K_A \times \text{Atot}}{K_A + \text{H}^+}$$

where $K_A = 4.0 \times 10^{-7}$, and Atot is in Eq/L (total protein in g/L x 0.0025)

Approximating the equation for electrical neutrality by ignoring the small effect of $[\text{H}^+]$, $[\text{CO}_3^{2-}]$ and $[\text{OH}^-]$:

$$\begin{array}{r} [\text{SID}] - [\text{HCO}_3^-] - [\text{A}^-] = 0 \\ 42 \quad - \quad 16.4 \quad - \quad 18 \quad = 7.6 \end{array}$$

which closely approximates the 8 mEq/L of lactate. Thus $[\text{SID}]$ is actually $42 - 8 = 36$. Either approach to this acid-base presentation is pretty straight forward and you can easily get to the diagnosis and treatment. Using the $\text{pH}/\text{PCO}_2/[\text{HCO}_3^-]$ relationships described above would still predict this as a mixed respiratory and metabolic acidosis.

Case 2

This was the same case but with a less dramatic acidosis, why? Is it any less serious?

$$[\text{Na}^+] = 138$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 100$$

$$[\text{SID}] = 42$$

$$\text{pH} = 7.377$$

$$\text{PCO}_2 = 35$$

$$[\text{HCO}_3^-] = 21.5$$

This time, the patient has a slightly lower than normal total protein concentration, likely from poor nutrition.

$$T_{\text{prot}} = 55 \text{ g/L which is equivalent to } [\text{A}_{\text{tot}}] \text{ of } 13.75 \text{ mEq/L or an } [\text{A}^-] \text{ of } 12 \text{ mEq/L}$$

Again looking at electrical neutrality

$$[\text{SID}] - [\text{HCO}_3^-] - [\text{A}^-] = 0$$

$$42 - 21.5 - 12 = 8.5$$

which again closely approximates the 8 mEq/L of lactate. The acid load is just as serious, but the loss of weak acid (hypoproteinemia) masks the severity of the acidosis. The message is:

The anion gap is mostly determined protein concentration. It may be equal to $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$, but it is not determined by that equation. **A change in total weak acid concentration will have no effect on $[\text{Na}^+]$, $[\text{K}^+]$ or $[\text{Cl}^-]$, but it will force a change in $[\text{HCO}_3^-]$ and 'the anion gap' in order to maintain electrical neutrality.** Thus, acid-base disturbances can occur secondary to a change in total protein concentration.

Case 3

Using the same numbers in a patient with more extensive hypoproteinemia secondary to mild congestive heart failure and nephropathy.

$$[\text{Na}^+] = 138$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 100$$

$$[\text{SID}] = 42$$

$$\text{pH} = 7.419$$

$$\text{PCO}_2 = 35$$

$$[\text{HCO}_3^-] = 23.7$$

This time the $T_{\text{prot}} = 45 \text{ g/L}$, corresponding to an $[\text{A}_{\text{tot}}]$ of just 11.25 mEq/L or an $[\text{A}^-]$ of 9 mEq/L .

Electrical neutrality:

$$[\text{SID}] - [\text{Lactate}] - [\text{HCO}_3^-] - [\text{A}^-] = 0$$
$$42 - 8 - 24 - 9 = 0 \text{ (almost)}$$

Notice how the low protein almost completely masks the severity of a metabolic acidosis. You might think that the patient was hyperventilating from pain more so than trying to compensate for a metabolic acidosis.

Other Examples

Example 1

The most common causes of acid-base disturbances are respiratory failure and changes in [SID]. Acute respiratory failure is straight forward. For example acute respiratory acidosis in the young asthmatic:

$$\begin{aligned}[\text{Na}^+] &= 138 \\ [\text{K}^+] &= 4 \\ [\text{Cl}^-] &= 100 \\ [\text{SID}] &= 42 \\ [\text{Tprot}] &= 80 \text{ g/L}, [\text{Atot}] = 20 \text{ mEq/L}\end{aligned}$$

$$\begin{aligned}\text{pH} &= 7.237 \\ \text{PCO}_2 &= 55 \\ [\text{HCO}_3^-] &= 24\end{aligned}$$

check for charge balance to confirm you are not missing anything:

$$\begin{aligned}[\text{SID}] - [\text{HCO}_3^-] - [\text{A}^-] &= 0 \\ 42 - 24 - 18 &= 0\end{aligned}$$

Example 2

The concept of acid-base disturbances being caused by changes in plasma protein concentration can be illustrated as follows:

Normal Protein Concentration

Electrolytes:

$$\begin{aligned}[\text{Na}^+] &= 138 \\ [\text{K}^+] &= 4 \\ [\text{Cl}^-] &= 100 \\ [\text{SID}] &= 42\end{aligned}$$

Total Protein:

$$80 \text{ g/L} = 20 \text{ mEq/L}$$

Acid-Base:

$$\begin{aligned}\text{pH} &= 7.365 \\ \text{PCO}_2 &= 40 \\ [\text{HCO}_3^-] &= 23.9 \\ [\text{A}^-] &= 18.1\end{aligned}$$

$$\begin{aligned}\text{PCO}_2 &= 55 \\ [\text{HCO}_3^-] &= 24\end{aligned}$$

Hypoproteinemia

$$\begin{aligned}[\text{Na}^+] &= 138 \\ [\text{K}^+] &= 4 \\ [\text{Cl}^-] &= 100 \\ [\text{SID}] &= 42\end{aligned}$$

$$40 \text{ g/L} = 10 \text{ mEq/L}$$

$$\begin{aligned}\text{pH} &= 7.501 \\ \text{PCO}_2 &= 40 \\ [\text{HCO}_3^-] &= 32.7 \\ [\text{A}^-] &= 9.3\end{aligned}$$

Example 3

The acid-base picture in chronic COPD is complicated by:

- i) chronic CO₂ retention is compensated by an increase in [SID] (usually by a low [Cl] (ref 1), consequently [HCO₃⁻] increases.
- ii) +/- hypoproteinemia

3a) *Chronic CO₂ retention in COPD with normal protein*

$$[\text{Na}^+] = 142$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 96$$

$$[\text{SID}] = 50 \text{ mEq/L}$$

$$[\text{Tprot}] = 80 \text{ g/L}, [\text{Atot}] = 20 \text{ mEq/L}$$

$$\text{pH} = 7.317$$

$$\text{PCO}_2 = 60$$

$$[\text{HCO}_3^-] = 32$$

Charge balance:

$$\begin{aligned} [\text{SID}] - [\text{HCO}_3^-] - [\text{A}^-] &= 0 \\ 50 - 32 - 18 &= 0 \end{aligned}$$

Predicted [HCO₃⁻] for chronic CO₂ retention is:

$$\begin{aligned} \Delta[\text{HCO}_3^-] &= 3.5(10 \text{ mmHg } \Delta\text{PCO}_2) \\ &= 3.5(60-40) \\ &= 7 \end{aligned}$$

$$[\text{HCO}_3^-] = 24 + 7 = 31 \text{ mMol/L}$$

Predicted pH for chronic CO₂ retention is:

$$\begin{aligned} \Delta\text{pH} &= 0.003(\Delta\text{PCO}_2) = 0.003(60-40) = 0.060 \\ \text{pH} &= 7.4 - 0.06 = 7.34 \end{aligned}$$

3b) Acute exacerbation of CO₂ retention in chronic COPD with normal protein

$$[\text{Na}^+] = 142$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 96$$

$$[\text{SID}] = 50 \text{ mEq/L}$$

$$[\text{Tprot}] = 80 \text{ g/L}, [\text{Atot}] = 20 \text{ mEq/L}$$

$$\text{pH} = 7.254$$

$$\text{PCO}_2 = 70$$

$$[\text{HCO}_3^-] = 32.4$$

Charge balance:

$$[\text{SID}] - [\text{HCO}_3^-] - [\text{A}^-] = 0$$

$$50 - 32.4 - 18 = 0$$

Predicted [HCO₃⁻] for chronic CO₂ retention:

$$\Delta[\text{HCO}_3^-] = 3.5 \times 3 = 10.5$$

$$[\text{HCO}_3^-] = 24 + 10.5 = 34.5$$

Predicted pH for chronic CO₂ retention:

$$\Delta\text{pH} = 0.003\Delta\text{PCO}_2$$

$$= 0.003 \times (70-40) = 0.09$$

$$\text{pH} = 7.4 - 0.09 = 7.31$$

3c) Acute exacerbation of chronic COPD plus metabolic acidosis (i.e. low [SID])

$$[\text{Na}^+] = 142$$

$$[\text{K}^+] = 4$$

$$[\text{Cl}^-] = 96$$

$$[\text{SID}] = 50 \text{ mEq/L}$$

$$[\text{Tprot}] = 80 \text{ g/L}, [\text{Atot}] = 20 \text{ mEq/L}$$

$$\text{pH} = 7.142$$

$$\text{PCO}_2 = 70$$

$$[\text{HCO}_3^-] = 25$$

Charge balance:

$$[\text{SID}] - [\text{HCO}_3^-] - [\text{A}^-] = 0$$

$$50 - 25 - 18 = 7 \text{ mEq/L}$$

You should be able to arrive within +/- 5 mEq/L of electrical neutrality. Any greater discrepancy should be investigated further. In this hypothetical case lactate accounts for the discrepancy. That is the [SID] is actually $50 - 7 = 42$ mEq/L. Thus a normal [SID] should cause concern in situations where you would not expect to find a normal [SID].

Predicted $[\text{HCO}_3^-]$ for chronic CO_2 retention:

$$\Delta[\text{HCO}_3^-] = 3.5 \times 3 = 10.5 \text{ mMol/L}$$

$$[\text{HCO}_3^-] = 24 + 10.5 = 34.5$$

Predicted pH for chronic CO_2 retention:

$$\Delta\text{pH} = 0.003(\Delta\text{PCO}_2)$$

$$= 0.003(70-40) = 0.090$$

$$\text{pH} = 7.4 - 0.09$$

$$= 7.31$$

3d) *Acute exacerbation of CO₂ retention plus low [SID] plus chronic hypoproteinemia*

$$\begin{aligned}[\text{Na}^+] &= 139 \\[\text{K}^+] &= 2.9 \\[\text{Cl}^-] &= 101 \\[\text{SID}] &= 41 \\[\text{Tprot}] &= 50 \text{ g/L}, [\text{Atot}] = 12.5 \text{ mEq/L}\end{aligned}$$

$$\begin{aligned}\text{pH} &= 7.222 \\ \text{PCO}_2 &= 70 \\ [\text{HCO}_3^-] &= 30.1\end{aligned}$$

Charge balance:

$$\begin{aligned}[\text{SID}] - [\text{HCO}_3^-] - [\text{A}^-] &= 0 \\ 41 - 31 - 9.5 &= 0.5\end{aligned}$$

Predicted $[\text{HCO}_3^-]$ for chronic CO₂ retention:

$$\begin{aligned}\Delta[\text{HCO}_3^-] &= 3.5 \times 3 = 10.5 \text{ mMol/L} \\ [\text{HCO}_3^-] &= 24 + 10.5 = 34.5\end{aligned}$$

Predicted pH for chronic CO₂ retention:

$$\begin{aligned}\Delta\text{pH} &= 0.003(\Delta\text{PCO}_2) \\ &= 0.003(70-40) \\ &= 0.09 \\ \text{pH} &= 7.4 - 0.090 = 7.31\end{aligned}$$

Usually it is safe to say that a high $[\text{HCO}_3^-]$ indicates a high $[\text{SID}]$. However, as this case illustrates low $[\text{Atot}]$ and a normal $[\text{SID}]$ can also result in a 'metabolic alkalosis'. If hypoproteinemia is suspected (history, physical exam, low albumin) then the influence of $[\text{SID}]$ on acid-base becomes more difficult to predict. The influence of the three independent variables on pH and $[\text{HCO}_3^-]$ is relatively straight forward when only one of the three is abnormal. However, changes in two or more independent variables are not simple to assess. In all cases though, if in doubt measure total protein - calculate $[\text{A}^-]$ and see if you get electrical neutrality. Any discrepancy from electrical neutrality suggests one of two possibilities:

- i) you are missing an anion
- ii) inherent variability of your measured variables, i.e. sodium and chloride are only accurate to +/- 2.5%, i.e. +/- 3 mEq/L for Na and +/- 2 mEq/L for Cl

If you do arrive at electrical neutrality then you can explain whatever acid-base disturbance you have. Think in terms of independent variables rather than wide gap, narrow gap, respiratory or metabolic disturbances. Once you know which of the independent variables is altered from normal focuses your thinking on underlying pathology.

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