Strong ion analysis at the bedside

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Abstract

Quantitative physicochemical models of human acid–base physiology filled a void between clinical acid–base analysis and general fluid physiology. Established approaches centred on the Henderson–Hasselbalch (HH) equation allow satisfactory bedside exploration of respiratory perturbations, but do not fully elucidate mechanisms of common non-respiratory 'metabolic' components. Though useful at the bedside, commonly used 'rules of thumb' that classify disturbances based on quantification of bicarbonate relative to CO_2 have also fostered a language that often misrepresents bicarbonate physiology. The physicochemical model is frequently perceived as too complex for bedside use, however a set of simplified screening questions based on Stewart's model can be utilized to aid acid-base interpretation. Examples using this approach are included in an online appendix. Emphasis is placed on understanding the consequences of hypoalbuminaemia, volume status, tonicity and chloride derangements as these are common in ICU patients.

Keywords Acid base physiology; carbon dioxide; clinical chemistry; hypoalbuminaemia; strong ion theory

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article, you should be able to:

- rapidly analyse the various elements contributing to plasma pH
- interpret clinical chemistry relevant to acid base
- explain the effects of hypo-albuminaemia and chloride on plasma pH
- explain the effects of tonicity on plasma pH
- discuss the role of bicarbonate in physiologic systems where CO_2 is abundant

The common emphasis on interpreting acid–base derangements using 'rules of thumb' and nomograms[2] (Figure 1) has resulted in clinicians having a detailed understanding of respiratory acid base disturbances, but often with a less precise concept of 'metabolic compensation'. Primary metabolic derangements are frequently presented as aetiological lists. However, disentangling the contribution of multiple pathologic processes and the effect of hypo-albuminaemia is frequently not attempted. Peter Stewart's mathematic approach to human acid–base physiology[1] provides significant clarification of metabolic disturbances, firmly anchoring acid–base within general fluid physiology.

In this review we utilize a set of dichotomous bedside questions with two simple calculations to utilize every time blood chemistry results are reviewed[3] (Figure 2). This approach may be used in conjunction with classic HH based rules-of-thumb or as a basis for more detailed quantitative analysis. This article describes the mechanisms behind this approach from where the HH equation leaves off. Rather than extensively explore Stewart's terminology such as A_{Tot} and SID (strong ion difference) interested readers are referred to in depth literature.[3,4]

Practice point

Figure 2 introduces a simplified strategy to rapidly identify the major contributors to plasma pH.

Hydrogen ions in context

The intracellular fluid (ICF) hydrogen ion concentration $[H^+]$ has critical effects on diverse chemical reactions and disproportionate effects on organ function. This pervasive influence despite miniscule concentration is a result of ionic hydrogen having the highest charge to molecular size ratio of all species in body fluids. The intracellular $[H^+]$ is tightly regulated with cytosolic concentrations (approximately 126 nmol/litre or pH 6.9[†]) being higher than extracellular fluid (ECF) concentrations (30 nmol/litre to 100 nmol/litre or pH 7.0 to 7.52).[5,6] For acid–base purposes, ionic charge is more important than concentration and for the remainder of this paper we will use the units milli or nano electrical equivalents per litre (mEq/litre or nEq/litre) when appropriate. For monovalent ions like H^+ or Na^+ these are numerically identical to the molar concentration; however, for divalent ions such as Mg^{2+}, concentrations in mmol/litre must be multiplied by 2 to convert to mEq/litre.

A strong ion is an electrolyte that fully dissociates in water into anions or cations. Weak electrolytes also have detectable quantities of undissociated molecules present in solution; with

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[†] $pH = -\log_{10}[H^+]$; $[H^+] = 10^{-pH}$. While easier to remember and communicate, pH does not convey how minute the concentrations of hydrogen ions are relative to other common electrolytes in physiologic systems.

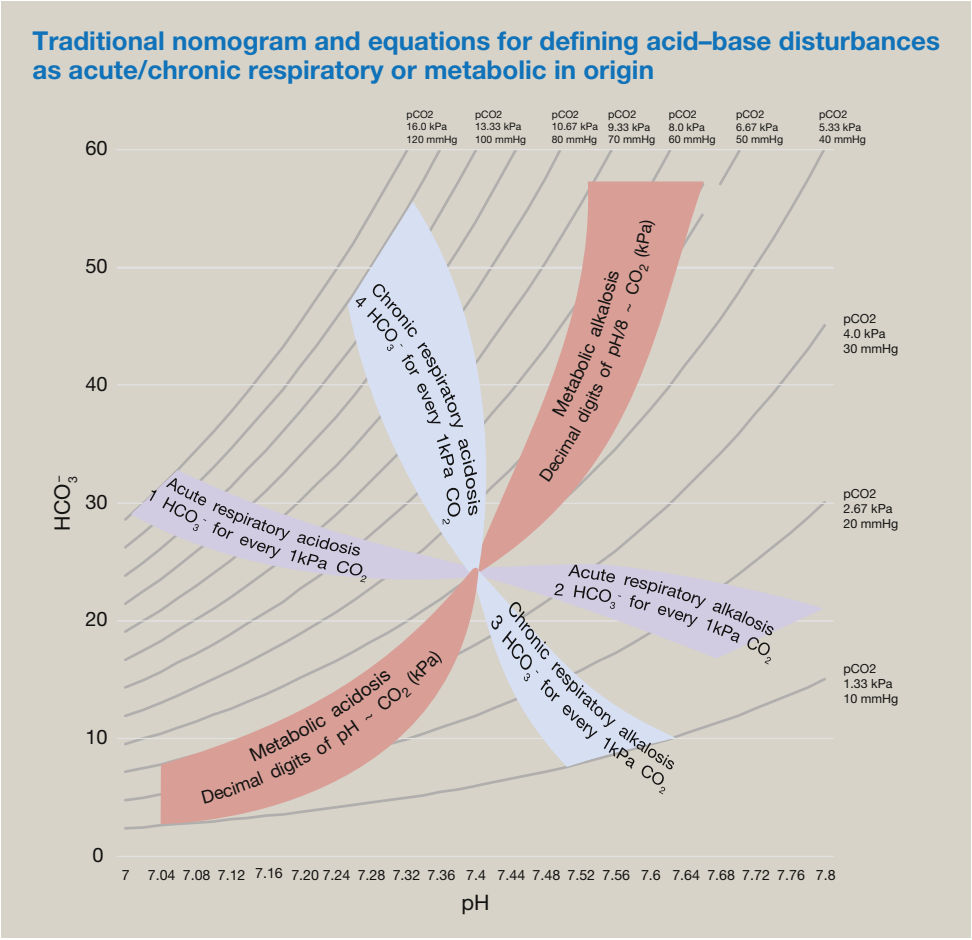

Figure 1 The background CO_2 curves (grey) plot the Henderson–Hasselbalch (HH) equation: entering any two parameters (from pH, pCO_2 and HCO_3^-) will result in the third. The shaded colour areas describe recognized patterns that the HH equation parameters trend toward in common disturbances. To aid in bedside analysis, relatively simple rules of thumb (text on chart) have been identified that describe these shaded zones. It is important to realise that the 'rules of thumb' are aides to recognize disorders. Note these versions of the 'rules of thumb' use pCO_2 in units of kPa.[13]

the ratio determined by the total electrolyte composition including $[H^+]$.

Measured plasma pH must be placed in the context of body fluid compartments and all the strong and weak electrolytes they contain (Figure 3). The large intracellular volume (ICF) comprises individual cells and as such comprises numerous independently regulated fluid pockets with similar composition.

Cellular metabolism within the ICF influences the composition of the 15–20 litre fluid volume[7] that comprises the ECF. Although the normal adult glomerular filtration rate (GFR) approximates 120 ml/min, only 1–3 ml/min of this actually leaves the body as urine with a composition dependent on the kidney's concentrating ability. This small urine volume equates to only 0.01% of the ECF volume per hour and thus limits the rate at which solutes can be removed from the body. Hence renal alteration of ECF composition including pH occurs over hours to days.[4]

Practice point

Plasma is in communication with the entire ECF making renal alteration of plasma electrolyte composition slow. It is urine production rate relative to ECF volume that determines the rate of change of measured electrolytes.

Carbon dioxide physiology

An adult consuming 300 ml/minute of oxygen with a respiratory quotient of 0.83 will produce and expire 250 ml/minute of CO_2. Henry's Law describes the solubility of carbon dioxide in plasma with a coefficient of 0.0308 mmol/litre/mmHg at 37°C decreasing to 0.0288 mmol/litre/mmHg at 40°C.[8] Thus an arterial $PaCO_2$ of 5.3kPa (40 mmHg) equates to a dissolved CO_2 of 1.232 mmol/litre$_{Blood}$ at 37°C.[8]

Only a fraction of CO_2 is transported as dissolved gas, the remainder is in chemical equilibrium with the dissolved phase through reactions with water for a total (ECF) content of nearly 500 ml/litre or 22.8 mmol/litre (Eq. 1 a–d). In blood, these reactions occur rapidly inside erythrocytes where the enzyme carbonic anhydrase (CA) is abundant.[9] A Cl^-/HCO_3^- membrane exchanger (the band 3 protein[8]) allows the resulting HCO_3^- to distribute through the remainder of the plasma and ECF.[8]

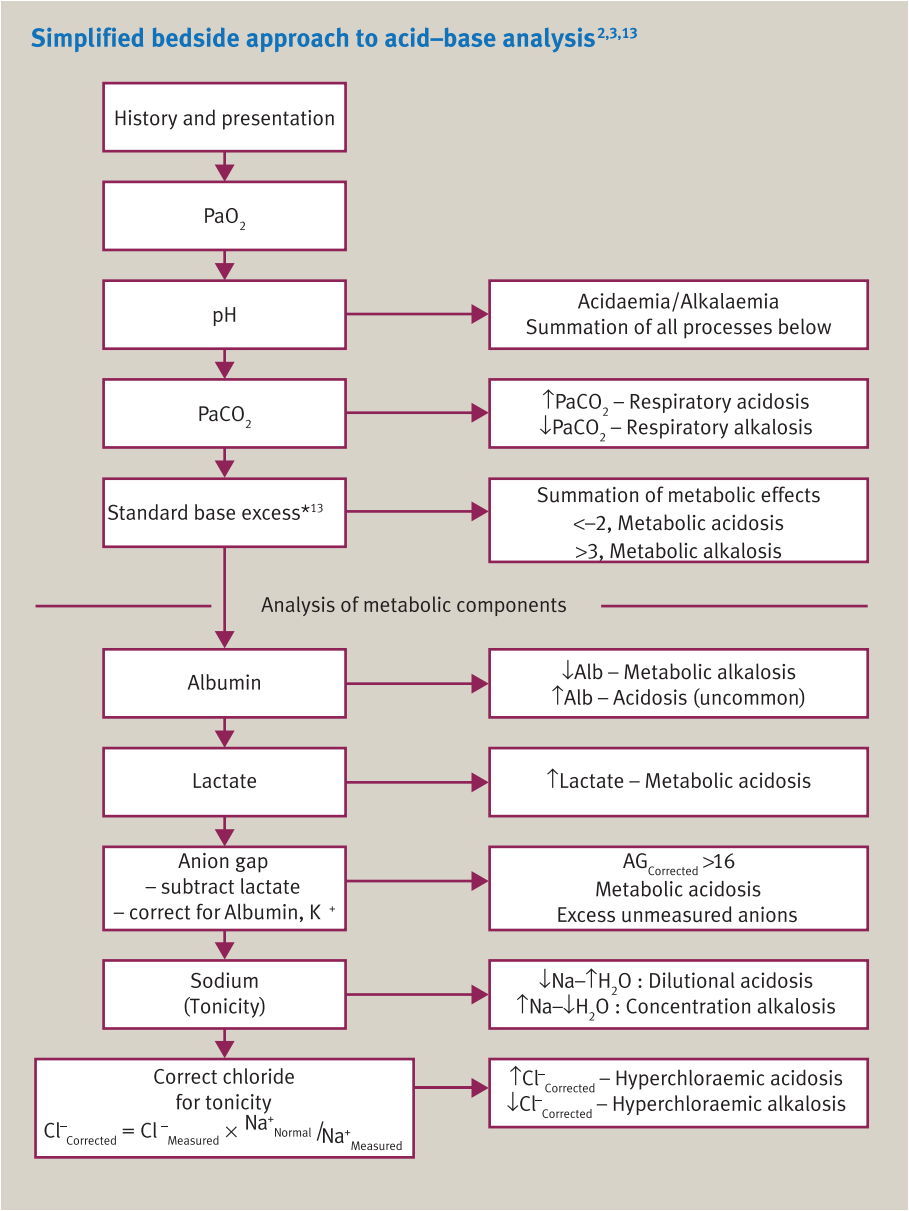

Figure 2 First evaluate and treat hypoxaemia - so called 'CO_2 retainers' have insufficient minute volume and may require ventilatory support – oxygen should never be with-held from hypoxic patients on this basis. Next the blood pH is described as acidaemic/alkalaemic – this is a summation of all contributing respiratory and non-respiratory acidifying and alkalinizing processes. The entire sequence should be followed each time; do not stop at a normal pH or normal CO_2 or else counter-acting metabolic processes such as hypoalbuminaemia with hyperchloraemia may be missed. Each step below 'pH' defines a qualitative acidifying or alkalinizing process that is contributing to the overall pH. Standard Base Excess is useful for identifying presence of metabolic disturbance but as a summation contributes little in analysing the aetiology. A widened anion gap leads to a search for a causative anion. See text for discussion and Online appendix for fuller description and examples.

$$
\begin{aligned}
CO_{2(gas)} + H_2O &\rightleftharpoons CO_{2(dissolved)} + H_2O && \text{a. Dissolving in water}\\
CO_{2(dissolved)} + H_2O &\underset{CA}{\overset{CA}{\rightleftharpoons}} H_2CO_3 && \text{b. Formation of carbonic acid}\\
CO_{2(dissolved)} + OH^- &\underset{CA}{\overset{CA}{\rightleftharpoons}} HCO_3^- && \text{c. Reaction with hydroxyl ion}\\
ptH_2CO_3 &\rightleftharpoons H^+ + HCO_3^- && \text{d. Dissociation to bicarbonate}\\
CO_{2(dissolved)} + R-NH_2 &\rightleftharpoons R-NH-COO^- + H^+ && \text{e. Formation of carbamino groups} \qquad (1)
\end{aligned}
$$

The measured pCO_2 of blood is the partial pressure that would result if equilibrium with a gas phase were to occur. In vivo blood has no gas phase, so Eq. 1b–d can be summarized by Eq. 2a[10] and rearranged to the logarithmic HH equation.[‡]

$$\begin{aligned} &CO_{2(\text{dissolved})} + H_2O \rightleftharpoons H^+ + HCO_3^- && \text{a. Summary Equation} \\ &[CO_2] \times \frac{K'}{[H^+]} = [HCO_3^-] && \text{b. Equilibrium Reaction} \\ &pH = pK' + \log \frac{[HCO_3^-]}{[CO_2]} && \text{c. Logarithmic Form} \end{aligned} \quad (2)$$

$$\text{At } 37^\circ : [CO_2]\text{mmol/L} = 0.0308 \times P_{CO_2}(\text{Henrys Law}),\ pK' = 6.09$$

$$\text{and } K' = 8.13 \times 10^{-7}\ \text{Eq.L}^{-1}.\text{mmHg}^{-1}$$

K′ is an experimentally derived constant for given temperatures and fluid compositions and describes the compound equilibrium of Eq. 1b–d. K' also incorporates the concentration of water molecules (55 moles/litre) which is orders of magnitude greater than the other reactants and hence considered constant as its concentration is negligibly affected by consumption in reactions.[10]

Of significance, the weak acid CO_2 and $[H^+]$ are the independent variables with the amount of CO_2 determined by metabolic production and pulmonary ventilation.[10] $[H^+]$ is in equilibrium with many other molecules. HCO_3^- concentration is always dependent on the amount of dissolved CO_2 and available $[H^+]$ by Eq. 2. Phrases such as 'the kidneys retain bicarbonate to compensate for chronic hypercapnoea' are over simplifications of nomograms and analytic methods for total CO_2[§]. Plasma, ICF, ECF and urine bicarbonate are dependent on the amount of local dissolved CO_2; manipulation of $[H^+]$ determines how much of this CO_2 exists as HCO_3^- in that fluid compartment. This manipulation of $[H^+]$ largely occurs by altering the composition of strong ions in each compartment.

Practice point

The Henderson–Hasselbalch equation summarizes the reactions of dissolved CO_2 and water, describing the amount of CO_2 stored as bicarbonate. CO_2 production is the primary independent variable in this equation. HCO_3^- is the dependent variable.

Effect of strong and weak electrolytes on CO_2 storage

CO_2 is lipid soluble; this property allows it to readily diffuse across cell membranes from regions of high concentration (mitochondria) to regions of lower concentration (ECF, plasma), culminating in crossing the alveolus to leave the body. In contrast, being charged, HCO_3^- can only cross membranes via ion exchange channels (Figure 3). The result is that in each compartment that CO_2 diffuses through, dissolved CO_2 and bicarbonate will exist in a ratio that depends on the concentrations of other strong and weak electrolytes whose dissociation determines the local $[H^+]$ by Eq. 2b. In culmination, this balance of charged species must also satisfy a requirement to maintain electrical neutrality and the ionization constant of water[10,3] (see Box 1: The dissociation of water and bicarbonate buffering).

The simplest summary of this complex interaction is that bicarbonate behaves as a rapidly adjustable electrical 'spacer' in an equation for electrical neutrality that operates in each fluid compartment (Eq. 3). *To emphasize this important concept: the large supply of dissolved CO_2 in a readily reversible reaction with water allows the negatively charged HCO_3^- concentration to rapidly rise or fall to maintain balance of positive and negative charge in each fluid compartment.* **

No other species in Eq. 3 can be shifted as rapidly from charged to uncharged (dissolved CO_2 gas) as bicarbonate. It is in this role as a charge 'spacer' that bicarbonate is a buffer i.e. without the weak acid CO_2 and hence without HCO_3^-, plasma pH

[‡] Occasionally the term αPCO_2 is used in this equation to describe the total concentration of CO_2 plus carbonic acid. However the concentration of carbonic acid is orders of magnitude smaller than CO_2 thus $[CO_2]$ can be calculated accurately from Henry's Law without alteration of the solubility constant.[10]

[§] Serum chemistry analysers measure the total volume of CO_2 liberated from a collected sample after addition of a strong acid. Misleadingly, this is frequently reported as serum bicarbonate rather than total CO_2. Blood gas analysers instead measure the pCO_2 and pH and calculate HCO_3^- from the HH equation. Because the acid addition method includes dissolved CO_2 the resulting HCO_3^- is normally 2–4 mmol/L higher than that from the gas analyser.[11]

[**] Being electrical neutrality of all species, the appropriate units are charge (milli-equivalents per litre mEq L^{-1}) hence the concentration of double valent ions in mmol/L is multiplied by 2 to account for their charge density. The multiplier of 1.8 for inorganic phosphate and 0.28 for albumin are useful approximations as the charge density for these weak acids varies slightly with pH but the effect is not substantial compared to the dissociation of CO_2[3] $[z^+]$ and $[x^-]$ refer to other unmeasured exogenous or endogenous cations (such as lithium) and anions (such as methanol, ethylene, glycol, etc.). $[H^+]$ is included but its concentration is orders of magnitude smaller than the other species.

$$\begin{aligned}&[Na^+] + [K^+] + 2 \times [Ca^{2+}] + 2 \times [Mg^{2+}] + [z^+] + [H^+] \\ &= [Cl^-] + 1.8 \times [PO_4^{2-}] + [HCO_3^-] + 0.28 \times [\text{Alb (g/L)}] + [\text{lactate}^-] + [XA^-] + [OH^-] \\ &\Updownarrow \\ &[CO_2] \times \frac{K'}{[H^+]} = [HCO_3^-]\end{aligned} \quad (3)$$

would be much *more* alkaline and more sensitive to alteration in electrolyte balance as the only other abundant molecule which can rapidly dissociate to maintain charge balance is water (see Box 1: The dissociation of water and bicarbonate buffering).

In contrast to the extensive supply of CO_2 that readily dissociates to bicarbonate, concentrations of other species in Eq. 3 cannot alter quickly due to the size of their containing fluid compartments (Figure 3) and the rate of renal solute removal. Tight regulation in other homeostatic processes also imposes limitations: sodium is regulated with tonicity and blood pressure, albumin exists in its own balance of production and catabolism, and the other cations and phosphate have low and tightly regulated extracellular concentrations. The exception is chloride that despite being unable to vary rapidly, can alter significantly over time to contribute significantly to negative charge.

Chloride freely enters glomerular filtrate but due to absence of plasma proteins (in health) and Gibbs–Donnan equilibrium, the filtrate chloride is around 5% greater than plasma while the filtrate sodium is around 5% lower[12] (Figure 3). Tubular chloride reabsorption occurs down electrochemical gradients developed by active reabsorption of cations and secretion of organic acids. Compared to plasma, increased tubular chloride concentration relative to sodium results in renal correction of acidotic states. CO_2 again freely diffuses across membranes and the presence of tubular carbonic anhydrase allows HCO_3^- to fill the resultant urinary charge space.

Practice point

The sum of positively charged electrolytes in each body solution must equal the sum of negatively charged electrolytes (this includes small ions, weak acids and bases, and charged amino-acid side chains in proteins). Being in equilibrium with CO_2 allows bicarbonate to rapidly adjust when an alteration of other charged species occurs.

Hypoalbuminaemia and metabolic alkalosis

Eq. 3 also describes the alkalinizing effect of hypoalbuminaemia and the necessity of correcting anion gap calculations for albumin.[10,3] Albumin is the most abundant plasma protein with normal concentrations around 40 g/litre; and contributes significantly to the negative charge pool. Albumin's electrical charge in mEq/litre is approximately one quarter of its concentration in g/litre (as a weak acid the precise fraction varies with pH however this approximation is adequate clinically).

In contrast to adding an anion such as lactate, lowering an anion such as albumin creates an anion deficit (a loss of negative charge). It is common at the onset of critical illness for serum albumin to abruptly decline to half the pre-morbid concentration within 2–3 days. By inspection of Eq. 3 in the absence of other anions, this loss of negative charge will be balanced by a shift of CO_2 to HCO_3^-, and at more minute concentrations a decrease in $[H^+]$ and increase in $[OH^-]$, that is, a metabolic alkalosis with raised HCO_3^- results (Box 1: The dissociation of water and bicarbonate buffering). In the absence of other abnormalities, over time a hyperchloraemia may be seen with HCO_3^- returning toward normal as the increased chloride balances the loss of negative charge due to hypoalbuminaemia. The situation is then better described as a hypo-albuminaemic metabolic alkalosis compensated by a hyperchloraemic acidosis. Similar effects may be observed to a lesser degree with other electrolyte excess/deficit such as hyperphosphataemia or lithium toxicity however the magnitude is lesser due to the much lower concentrations relative to the more prevalent electrolytes.

Practice point

A low albumin has an alkalinizing effect on plasma; if low albumin exists with normal pH there must be a co-existent acidifying process abnormality, often this is hyperchloraemia.

Screening for unmeasured anions with the anion gap

The anion gap (AG) is a simplified version of the full equation for electrical neutrality shown above (Eq. 3). The AG is used to screen for additional pathologic weak acids (XA^-).

$$\text{Anion Gap} = [Na^+] - [Cl^-] - [HCO_3^-] \quad (4)$$

Like Eq. 3, the units are charge (i.e. mEq/litre) and if normal electrolyte concentrations are used then the normal AG is 10–16 mEq/litre. Elevated values suggest an excess of unmeasured anion such as lactate, toxins (methanol, ethelyne glycol), ketoacids, or accumulating metabolites in renal failure. The clinical scenario will determine the need to identify the anion.

As the anion gap measures a charge space, concentrations of known anions can be numerically subtracted to clarify an abnormality. For example, the lactate concentration should be subtracted from an elevated anion gap to determine if it normalizes to 10–16 mEq/litre. If it does the lactate was the primary cause, if the AG remains elevated then other unmeasured anion(s) are contributing. Similarly, known abnormalities of cations such as hyperkalaemia (add the amount it is elevated by) or lithium ions

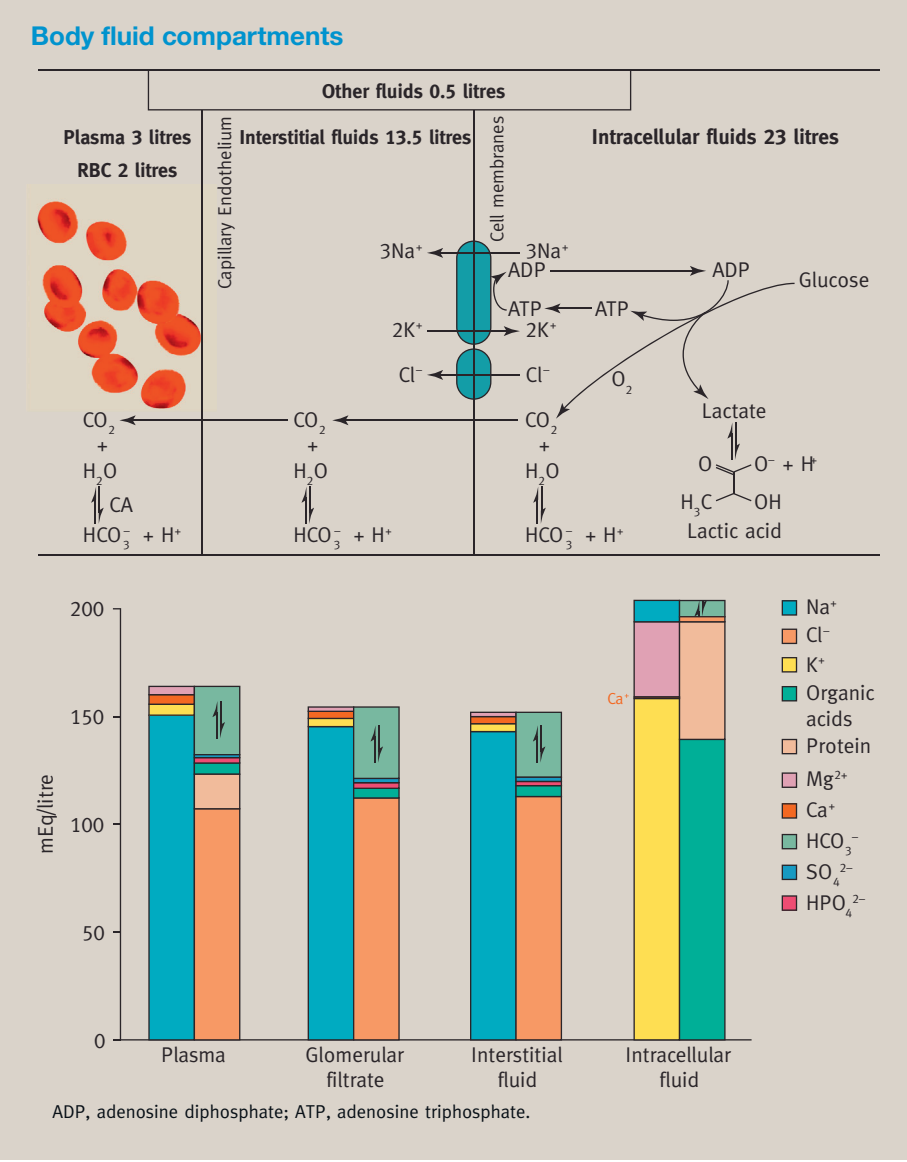

Figure 3 Top panel, idealized body fluid compartments in a 70 kg adult[7] with energy requiring Na^+K^+ATPase membrane pump supplied with ATP from metabolism of glucose. Bottom panel demonstrates composition of fluid compartments.[12] Electrolytes may be considered to interchange freely between plasma, and interstitial fluid and glomerular filtrate however proteins (mainly albumin) are largely confined to plasma. Charge differences may exist between compartments but within compartments cumulative positive and negative charge must be balanced. Dissolved carbon dioxide easily diffuses across lipid membranes and dissociates in each compartment to HCO_3^- with the final concentration depending on the overall charge space in that compartment (see Eq. 3). Figure compiled from multiple sources.[1,12,7,14]

(z^+ in Eq. 3) may offset an abnormal acid and should be added to the $[Na^+]$ before subtracting $[Cl^-]$ and $[HCO_3^-]$.

The simple AG must be adjusted if hypoalbuminaemia is present as the alkalinizing effect described above will mask the presence of pathologic acids (see above). The approximation that albumins charge in mEq/litre is ¼ of its concentration in g/litre is again utilized:

$$AG_{Corrected} = AG_{Measured} + \frac{\text{Normal albumin (g/L)} - \text{Measured albumin (g/L)}}{4} \quad (5)$$

Practice point

The negative electrical charge on unmeasured weak anions usually results in a shift of bicarbonate (acutely) and/or chloride (slowly) and is thus detected by the anion gap. The sensitivity of anion gap is significantly improved by correcting for albumin.[3]

Correcting chloride for altered tonicity

Sodium is the dominant extracellular cation and chloride is the dominant extracellular anion. The concentration difference between these two strong electrolytes contributes most to ECF

The dissociation of water and bicarbonate buffering

The dissociation of water is described by Eq. 7. Pure water has a concentration of about 55 moles/litre, in comparison the concentrations of H^+ and OH^-in pure water are 1.0×10^{-7} Eq/litre (pH 7) implying a very small dissociation constant, K_w, of 4.3×10^{-16} Eq/litre at 25°C. The magnitude of this difference, the concentration of water and K_w are combined into a single constant: K'_w.

$$\begin{aligned} &H_2O \rightleftharpoons H^+ + OH^- && \text{a.}\\ &[H^+] \times [OH^-] = K_w \times [H_2O] && \text{b.}\\ &\text{where } K_w = 4.3 \times 10^{-16} \text{Eq/L at } 25^\circ C && \\ &[H^+] \times [OH^-] = K'_w && \text{c.}\\ &\text{where } K'_w = 1 \times 10^{-11} \text{mEq/L at } 25^\circ C && \end{aligned} \tag{7}$$

It seems counter-intuitive that dissociation of a neutral H_20 molecule into two oppositely charged species can be involved in any other reaction of electrical neutrality involving other charged species. However, what Eq. 7c states is that as along as hydrogen concentration multiplied by the hydroxyl concentration equal K'_w their individual concentrations need to be equal and is best illustrated using a (simplified) stoichiometric example: Consider mixing two solutions: 500 mL of 0.3M sodium hydroxide and 500 mL of 0.2M hydrochloric acid. The resulting 1L solution contains the following charged species and as these are strong ions they will be fully dissociated (ie no NaOH or HCl molecules will be present, only the cations and anions):

$$\begin{aligned} &150 \text{ mmol } \quad NaOH \rightarrow Na^+ + OH^-\\ &100 \text{ mmol } \quad HCl \rightarrow Cl^- + H^+\\ &150 \text{ mEq } Na^+ + 100 \text{ mEq } H^+ = 250 \text{ Total positive mEq}\\ &150 \text{ mEq } OH^- : 100 \text{ mEq } Cl^- = 250 \text{ Total negative mEq} \end{aligned} \tag{8}$$

Inspection reveals the total positive charge is balanced by negative charge. However, these ions exist in a much larger volume of water molecules whose equilibrium cannot be ignored. Eq. 7 states that the product of [H^+] x [OH] = 1×10^{-11} (K'_w) implying firstly that OH^- and H^+ almost entirely combine to form water molecules and secondly that if the concentration of [OH] exceeds [H^+] then the [H^+] concentration must be extremely small. In our 1L solution described by Eq. 8 we have 150 mEq of OH^-, 50 mEq in excess of the H^+ so after applying the equilibrium constraints of Eq. 7c the concentration of H^+ will be extremely small (K'_w $1 \times 10^{-11} \div H^+$ $50 \times 10^{-3} = H^+$ 2×10^{-10} mEq/litre i.e. a pH of 9.7). The reactions and final concentrations that need consideration are listed in Eq. 9 and include the secondary reaction where the combined H^+ and OH^- form nearly 100 mmol of water.

$$\begin{aligned} &150 \text{ mmol } \quad NaOH \rightarrow Na^+ + OH^-\\ &100 \text{ mmol } \quad HCl \rightarrow Cl^- + H^+\\ &100 \text{ mmol } \quad H^+ + OH^- \rightleftharpoons H_2O \text{ (or approx. 1.8mL added to the 1L water solution)}\\ &150 \text{ mEq } Na^+ + \text{negligable } \left(2 \times 10^{-10}\right) \text{ mEq } H^+ = 150 \text{ mEq positive mEq}\\ &50 \text{ mEq } OH^- + 100 \text{ mEq } Cl^- = 150 \text{ mEq negative mEq} \end{aligned} \tag{9}$$

If we now bubble CO_2 gas through this solution and leave it in a sealed container where the gas above the solution is entirely CO_2 then by Eq. 1 the following reactions occur:

$$\begin{aligned} &150 \text{ mmol } \quad NaOH \rightarrow Na^+ + OH^-\\ &100 \text{ mmol } \quad HCl \rightarrow Cl^- + H^+\\ &50 \text{ mmoL } \quad CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-\\ &50 \text{ mmol } \quad H^+ + OH^- \rightleftharpoons H_2O \text{ (or approx. 0.9mL)}\\ &150 \text{ mEq } Na^+;\ 50 \text{ mEq } HCO_3^-;100 \text{ mEq } Cl^-\\ &2.19 \times 10^{-8} \text{ mEq } H^+ (\text{pH} = 7.66);\ 4.6 \times 10^{-4} \text{ mEq } OH^- \end{aligned} \tag{10}$$

In Eq. 10 when the dissociation of CO_2 occurs, H^+ and HCO_3^- result. The resulting H^+ reacts with the 50mEq of OH^- to form H_2O and again satisfy K'_w. *The net result is the dissolved weak acid CO_2 has lowered the pH (acidified) the solution from a pH of 9.7 to a pH of 7.66.*

This is the true buffering effect of bicarbonate when a reservoir of dissolved CO_2 is present: it provides an alternative anion to OH^- (provided by water dissociation) to balance positive charge. The charge 'space' created by the differing concentrations of the two strong ions Na^+ and Cl^- (i.e. the Strong Ion Difference; SID) was initially filled by OH^- making an extremely basic solution. If more sodium hydroxide were added (making the difference between strong cations (Na^+) and strong anions (Cl^-) greater) — as long as a source of CO_2 is present then the carbonation reaction will continue until the excess positive charge is balanced minimizing the rise in pH.

Much more CO_2 can be stored in solution (as bicarbonate) when an excess positive charge is present, hence we have medical sodium bicarbonate — it is the excess of positive charges on sodium that allows 50 mEq of bicarbonate to be in solution. Finally as the carbonation reactions are reversible, if we now purged our container with oxygen continuously until no CO_2 was detectable then we would return to the state of Eq. 9 where OH^- balanced

the charge difference i.e. as the CO_2 disappeared the solution would return to the very alkaline pH 9.7. This why medical sodium bicarbonate comes in glass ampules, CO_2 diffuses out through plastics and the result would be an ampule of sodium hydroxide.

Dilutional acidosis and contraction alkalosis

Consider again our 1000mL solution from Eq. 9 and add a further 500mL of 0.3M NaOH and another 500mL of 0.3M HCl, i.e. an additional 150 mEq of NaOH and 150 mEq of HCl. This will result in a 2000 mL solution with the following strong ion composition:

$$\begin{array}{l}\text{Original solution: 150 mEq } Na^+ \text{ and 100 mEq } Cl^-;\ 1000mL\\ +\\ \text{Added strong ions :150 mEq } Na^+ \text{ and 150 mEq } Cl^-;\ 1000mL\\ \Downarrow\\ \text{300 mEq } Na^+ \text{ and 250 mEq } Cl^-;\ \text{in 2000mL}\\ \text{Resulting concentration: } [Na^+] = 150mEq/L \text{ and } [Cl^-] = 125mEq/L\end{array} \quad (11)$$

The difference in charge concentration is now only 25 mEq/litre because although we added equal amounts of sodium and chloride ions, the proportional change of Cl^- was greater. In similar fashion to Eq. 9 we can demonstrate that our 2000 mL solution totals 300 mEq of OH^- and 250 mEq H^+ dropping the excess OH^- to 25 mEq/litre. Again K'_w determines the $[H^+]$ which has risen to 4×10^{-10} (pH 9.40).
The addition of equimolar 500 mL quantities of NaOH and HCl is equivalent to adding a 1000mL 0.9% normal saline solution and demonstrates the pH alteration (acidosis) resulting from the chloride concentration changing proportionally more than sodium: a hyperchloraemic acidosis.
These examples using simple solutions are provided to conceptualize blood plasma where strong cations (mostly sodium) exceeds strong anions (mostly chloride). Application of significant volumes of fluids with unphysiologic high chloride concentrations (such as 0.9% saline) alter the charge space and hence pH. What we have described is termed expansion acidosis, similar workings can be described for contraction alkalosis.

Box 1

charge space. The physiologic control of sodium is largely driven by blood pressure and tonicity. Abnormalities of Na^+ concentration imply water excess or deficit and from an acid base perspective suggests altered concentration of all charged species. The simplest solution to determine the net effect is to correct the chloride for tonicity:[3]

$$Cl^-_{Corrected} = Cl^-_{Measured} \times \frac{\text{Normal Sodium (mmol/L)}}{\text{Measured Sodium (mmol/L)}} \quad (6)$$

$Cl^-_{Corrected}$ is then compared to the normal chloride reference range to identify whether it is inappropriately high (i.e. hyperchloraemic metabolic acidosis) or low (hypochloraemic metabolic alkalosis). It must be emphasized that this correction is not used in calculating anion gap − the measured value is then appropriate as exists in Eq. 3; the $Cl^-_{Corrected}$ simply allows ready identification of hyper-/hypo-chloraemia when serum $[Na^+]$ is abnormal. Alterations of corrected chloride commonly occur whenever fluids that contain a sodium:chloride ratio different to normal plasma enter or leave the body (see Box 1) such as 0.9% normal saline which contains 150 mmol sodium and 150 mmol of chloride, the latter being significantly higher than normal plasma chloride.

Practice point

As the predominant ECF anion, chloride contributes significantly to electrical neutrality and should be considered relative to sodium. Abnormalities may be acute (often gastro-intestinal chloride loss or elevated from 0.9% saline administration) or delayed (e.g. hypochloraemia from loop diuretics or renal ECF correction in other acid-base deviations).

Conclusion

We have explored the mechanisms behind a simplified approach to bed−side acid−base disturbances (Figure 2) that incorporates components of the physicochemical approach to further elucidate the effect of common metabolic disturbances frequently seen in the critically ill such as hypo-albuminaemia, tonicity and chloride disturbances. Identifying these processes without quantification is useful in determining severity of disturbances and metabolic contributions, for example a low pH (acidaemia) with a low albumin (in isolation resulting in alkalosis) marks more severe underlying derangements than a low pH with a normal albumin. ◆

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mpaic.2019.09.004.

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