CHAPTER 65

Acid-Base Physiology and Diagnosis of Disorders

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OBJECTIVES

This chapter will:

1. Review in depth and criticize some of the foundations for current acid-base discourse.
2. Describe a model based on the strong requirement for charge balance in any fluid. To facilitate this, the notion of strong ion difference, which is the difference in concentrations between totally dissociated bases minus totally dissociated acids, is employed. It will be demonstrated that the strong ion difference is integral to classic understanding of acid-base transport.
3. Discuss physiologic and clinical applications and theoretical objectives.
4. Provide a short practical section that shows how diagnoses can be refined and explicitly analyzed on the basis of the discourse.

   Repeatedly, areas of uncertainty and in need for fresh investigation are pointed out. Supplementary notes are available with code to reproduce some of the findings from https://figshare.com/articles/Critical_care_nephrology_chapter_65_Acid–Base_physiology/4231364/1

Traditional acid-base modeling has developed in two main directions. One proposes integrated whole-body acid-base balance based on indirect accounting of acid fluxes and separating endogenous acid production, renal acid excretion, and intestinal alkali absorption.[1] The other current tradition has focus on individual transporters and is particularly well developed in the renal domain.[2] Although frequently presented side to side,[3] these discourses have not been integrated, and quantitative understanding is fragmented.

In this chapter acid-base physiology is developed with a focus on explaining why pH in any fluid has exactly the observed value. In the current discourse, pH is a function of the balance of movements of protons in and out of the fluid.[2,4] An older tradition, which we will revive, emphasized the requirement for charge balance in any fluid and on that basis formulated algorithms for finding H^+ and pH.[5–7]

It frequently is stated that multiple regulatory systems attempt to keep pH at control value.[4] However, it appears that the control systems respond to physical effects of pH or H^+ rather than to pH or H^+ as such. This is more than a semantic argument, as can be seen, for instance, in the discussion of the effect of temperature on acid-base status.[8] One position states that hypothermic patients should be alkaline just because of the effect of temperature on dissociations of buffers and water without invoking any actual transport of protons,[9] and another discourse holds that only changes in transporter settings can alter pH.[4] As will be seen, formulating acid-base physiology in terms of charge balance will lean heavily toward the former standpoint. Likewise we shall see examples of the fact that frequently it is more the circumstances and mechanisms of, say, acidosis that explains the morbidity rather than it is the actual pH.

A problem related to the question of what is regulated obviously is what is sensed by cells and organs.[10] A recent important trend is that one of the universal "acid" sensors, the soluble adenylyl cyclase, is sensitive directly[11] to HCO_3^- in a completely pH-independent way.[12] This arrangement has several advantages related to the faster movement of HCO_3^- than of H^+ in the cytosol and direct link to metabolism in Krebs cycle and mitochondria.[13]

The concept of buffering is paramount for conventional acid-base modeling,[14] and it is revealing that the classical results can be obtained directly from the charge-balance model, which also, however, exposes crucial dependencies on strong ions, ignored in the classical discourse.

Also, by explaining buffering, we examine the connections between the proton-focused discourse and the charge-balance paradigm to show that some of the disagreements are mainly apparent because strong ions are implicated in both discourses.

CONVENTIONAL COMPREHENSIVE ACID-BASE MODEL

The standard textbook paradigm of acid-base physiology attempts quantification by observing fluxes of substances

perceived to generate or neutralize protons.[1,14] These are endogenous acid production, renal net acid excretion (NAE), and net gastrointestinal alkali absorption. Renal NAE is classically calculated as the sum of ammonium (NH_4^+) and titratable acidity (TA) less excreted bicarbonate (HCO_3^-):

$$NAE = NH_4^+ + TA - HCO_3^-$$

It can be shown[15] that the model[1] is misspecified, because it leads to the absurd prediction that urine will carry a negative net charge under the development of acidosis from a whole-body perspective. Therefore NAE is also in doubt because it has never been quantitatively validated but rather has been discredited in experimental studies,[16] demonstrating that NAE as calculated conventionally is unrelated to acid-base status. In practice it is not a large problem because the textbook model has never been used in clinical practice.

In contrast, the model for acid-base physiology based on charge balance proposes instead that pH in any compartment is a function of strong ions, weak acids, and pCO_2. When looking to the kidneys it is clear that they are instrumental in regulating primarily the homeostasis of electrolytes. It always has been problematic for physiology how the kidneys could integrate these requirements with the necessity of regulating also acid-base.[16,17] From the viewpoint of charge-balance this conflict is apparent only because the kidneys regulate acid-base by way of regulating electrolytes, because titratable acidity and ammonium excretion are expressed fluently in terms of strong ions.

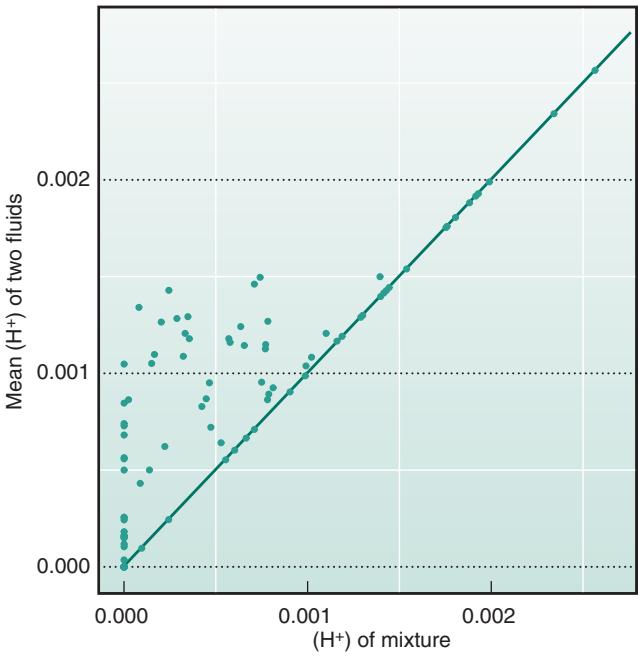

FIGURE 65.1 The composite H^+ in a fluid mixed 1:1 from two fluids with SID taken randomly between –3 mM and +3 mM is unpredictable from H^+ in the constituent fluids.

CHARGE-BALANCE BASED MODELING OF ACID-BASE

The charge-balance concept is based on the strong requirement that positive and negative charges are equal, because otherwise very big potentials develop. Apart from strong ions, which have pH independent charges, chemistry defines how pH determines all other charges. Thereby pH can be obtained based on total concentrations of fluid constituents.

It is important to acknowledge that this balance pertains strictly to macroscopic fluid in balance, whereas microscopically, across membranes, or close to electrogenic transporters, voltages certainly develop.[18] However, the concept is equally useful because these forces on the microscopic level are instrumental in energizing the transports[19] that eventually make for macroscopic balance, and even on the microscopic level, the observed voltages require only very small charge imbalances (e.g., to generate a potential of 60 mV across an axon with diameter 10 µm requires separation of less than 1/40,000 of cytoplasm K^+ as demonstrated by Wright).[18]

To develop the model, a large pool of H^+ is contributed from water dissociation. It has been stated that water dissociation should be irrelevant to acid-base, because a proton and hydroxyl ion always are contributed together. Elaborating further isn't necessary, the author suggests assembling a consistent model[7] including water dissociation and examining its utility.

Water Dissociation

$$k_w = [H^+] * [OH^-]$$

Equation 1

There is considerable discussion of the actual form in which H^+ is present in water with the hydronium (or Eigen) ion H_3O^+ being the common favorite, although recent studies[20] support $H_{13}O_6^+$. Nonetheless exchange of single protons occurs,[21] and the extra charge is unavoidable irrespective of its associations, so the model provided here will be invariant regardless.

Charge Balance With SID

$$SID + [H^+] - \frac{K'w}{[H^+]} = 0$$

$$[H^+] = -\frac{SID}{2} + \sqrt{\left[\left(\frac{SID}{2}\right)^2 + K'w\right]} = 0$$

Equation 2

An initial theoretical experiment is performed to demonstrate the crucial fact that H^+ in biologic fluids is not as easily identified as Na^+, for example.[7] The example is employed in Eq. 2 with two fluids randomly sampled with SID between –3 mM and 3 mM, which were mixed 1:1. The mean values of H^+ and pH were compared with the corresponding values in the mixture. As is seen from Figs. 65.1 and 65.2, H^+ and pH in the most simple mixture are not predictable from the H^+ and pH in constituent fluids.

Supplementary Note 1
Monovalent Weak Acid

$$[H^+] * [A^-] = k_a * [HA] \quad \text{dissociation of weak acid}$$

Equation 3

$$[Atot] = [HA] + [A^-] \quad \text{total concentration}$$

Equation 4

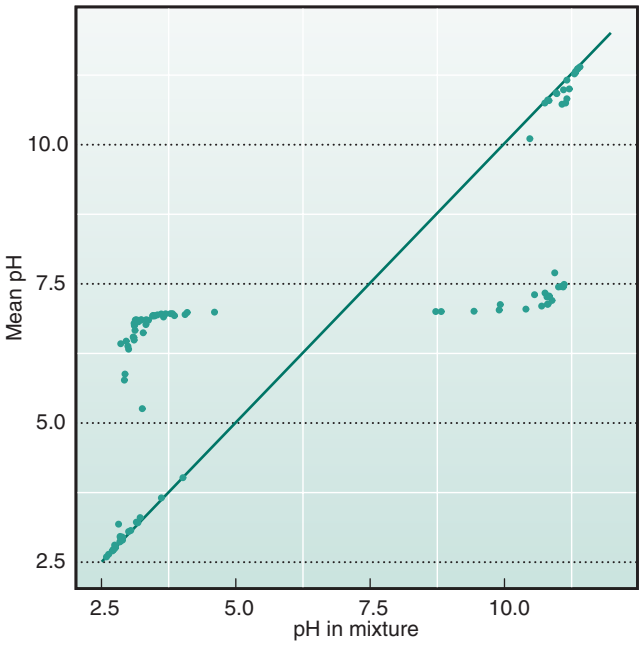

FIGURE 65.2 The composite pH in a fluid mixed 1:1 from two fluids with SID taken randomly between −3 mM and +3 mM is unpredictable from pH in the constituent fluids.

$$[A^-] = \frac{k_a * [Atot]}{k_a + [H^+]} \quad \text{calculated charge}$$

Equation 5

Charge Balance

$$[H^+] + SID - \frac{K'w}{[H^+]} - \frac{K_a * Atot}{[H^+] + K_a} = 0$$

Equation 6

Here *SID* (strong ion difference) is the difference between concentrations of totally dissociated base and totally dissociated acid, *K′w* is the water dissociation constant, K_a is the weak acid dissociation constant, and *Atot* is the total concentration of weak acid. SID constituents and total concentration of weak acids, Atot, can be measured and predicted directly, and from that, proton concentrations can be operationalized. Proton concentrations thereby are explicit functions of the other charged moieties, and indeed any missing entry can be found given the others.

Generalization of this relationship to include multiple buffers and the effect of CO_2 using the principles above is straightforward physical chemistry, yielding equations such as Eq. 7, explained and derived in Ring and Kellum.[22]

$$[H^+] + SID - \frac{K'w}{[H^+]} - \frac{k_c * pCO_2}{[H^+]} - \frac{2 * k_3 * k_c * pCO_2}{[H^+]^2} - P * \left(1 + \frac{k_2}{k_2 + [H^+]}\right) - Alb * AF + [H^+] * Alb * \left(\frac{AH}{k_h + [H^+]}\right) - \sum \frac{k_a * Atot}{k_a + [H^+]} + \sum \frac{[H^+] * k_b * Btot}{[H^+] * k_b + k_w} = 0$$

Equation 7

Here *P* is total phosphate, and the contributed charge is focused on the second dissociation constant (including all three dissociations has no effect in biologic fluids but is covered in supplementary material). The effect of albumin is modeled after Watson[23] with fixed negative charges (AF) and weak base effect (AH). Atot is arbitrary weak acid and Btot arbitrary weak base.

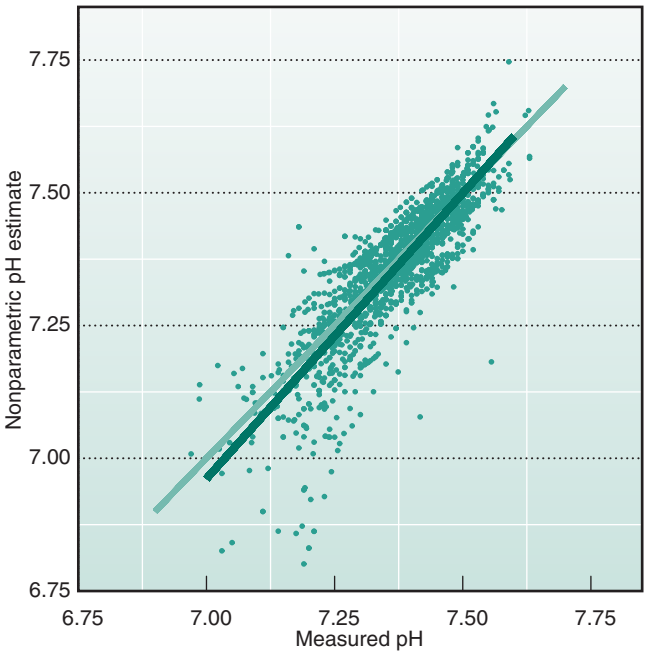

FIGURE 65.3 Nonparametric predicted pH values compared with measured pH values from reference 21. *The thin line* indicates identity (x = y); *thick line* indicates the linear fit. For details see reference 21.

To understand how the model could be efficient in finding H^+ in the nanomolar range on the basis of the charge on species with measurement errors on a much larger scale, it is noteworthy that in Eq. 7 protons occur mainly in the denominators together with very small constants so that they end up having a great impact on calculated charge balance. This is also easily confirmed by simulation. We have reported how well pH is found based on all other measured charges in a sample of 2500 blood tests,[22] and further practical confirmation of the construct has been provided.[24,25]

Figure 65.3 shows modeled versus measured pH. Including a correction for ionic strength further improves the fit, and here accounting for possible error in measured pH is made by nonparametric methods, as explained in reference 22. On this basis, and on the basis of physical chemistry from which the expressions are derived, it can be concluded that H^+ and pH are an explicit function of the other measured charges.

Using Eq. 7 we can simulate over a range of strong ion difference (SID), albumin, P, and pCO_2 how pH is a function of measured moieties. From Fig. 65.4 it is evident how the four variables affect pH. It can be seen that as pCO_2 increases, pH declines as expected, and as SID increases, pH likewise increases. Also, and perhaps less intuitively, pH declines as albumin or phosphate increases.

It can be concluded that H^+ and pH are related closely to the other charges, and therefore a change in pH will result when any of these components change.

Also it is evident from Eq. 7 that there is no hierarchy between dependent and independent variables. To use that fact and at the same time further bolster the utility of the model (e.g., Equation 7) and make preparation for the treatment of renal regulation of acid-base, we will present

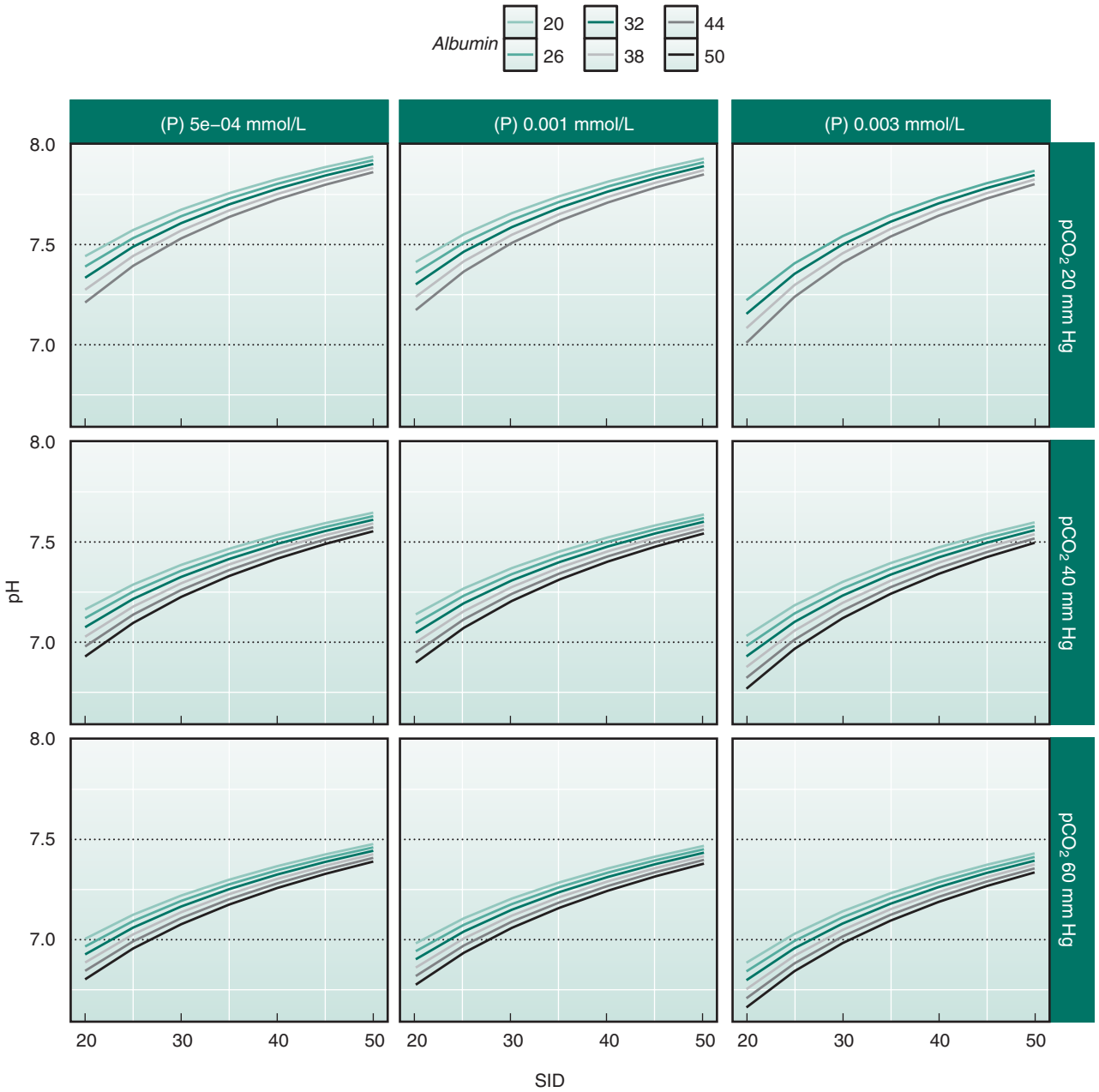

FIGURE 65.4 Simulated pH values from Eq. 7 as a function of SID, pCO_2, albumin, and phosphate. pCO_2 and SID are the dominant forces.

data from 1945 from Pitts and Alexander[26] also analyzed in Ring and Kellum.[22]

A total of 24 experiments were made on four dogs. Titratable acidity was measured as the amount of strong base added urine to obtain plasma pH, as defined by Henderson,[27] and reported together with pH and concentrations of phosphate and creatinine in final urine and plasma pH. From Eq. 7 (creatinine modeled as weak base with K_b as $10^{14-4.97}$; pKa 4.97, according to Pitts[26]) given urine [P], urine [creatinine] and pH, we can find SID and with the same concentrations to calculate the SID at plasma pH. Subtracting these gives an estimate of titratable acidity, which requires Eq. 7 to be correct. The mean value for observed titratable acidity was 0.242 mmol/min compared with 0.245 mmol/min as calculated based on Eq. 7 (p = .893, 95% CI for difference –0.061 mmol/min to 0.054 mmol/min, the correlation between the values was 0.999). Therefore from these old results further substantiation of the charge balance model of acid-base is achieved.

EXPLORING THE UTILITY OF THE CHARGE-BALANCE MODEL TO UNDERSTAND ACID-BASE

Pivotal to the traditional understanding of acid-base is the concept of buffering capacity,[4] defined as

$$\beta = \frac{dSID}{dpH}$$

meaning that an infinitesimal concentration of strong acid or base is added and the resulting change in pH is registered.

To measure a flux of protons therefore, β is multiplied by the shift in pH, forming

$$Flux = \int_{pH_1}^{pH_2} \frac{dSID}{dpH} dpH = \Delta SID$$

To give a concrete application and further prepare for handling of renal acid-base regulation we will present how intracellular pH regulation can be understood in terms of the charge-balance discourse.

Modeling Intracellular pH

A generic intracellular composition is taken from Magder[28]:

Total buffer (A_{tot}) is at 200 mM, Ka = $10^{-6.8}$, pCO_2 = 40 mm Hg, and SID is varied from 80 to 180 mM. pH is modeled from Eq. 8 (a simplification of Eq. 7):

$$[H^+] + SID - \frac{K_w}{[H^+]} - \sum \frac{K_a * Atot}{K_a + [H^+]} + \sum \frac{K_b * Btot * [H^+]}{K_b * [H^+] + K_w} - KC * \frac{pCO_2}{[H^+]} - 2KC * K3 * \frac{pCO_2}{([H^+])^2} = 0$$

Equation 8

Here everything is known, so we can at any SID find pH, and then add infinitesimal change in SID of 1 nM and find the new pH, and thereby β. Hence is found BC versus pH.

Supplementary Notes 2a and 2b

Traditionally[29] β is found using NH_4Cl added in the test tube, and in attached files in supplementary notes 2a+2b it is shown that this exactly reproduces the found β. Now we make an experiment, changing intracellular pH in a known way (Figs. 65.5 and 65.6).

Dividing the time into very small intervals, take the middle of these and the corresponding pH_i, and find in the curve of β versus pH_i the relevant β, multiply and sum it all to yield 81.5398 mmol/L. Looking now at the initial and final pH of 6.6 and 7.494, using Eq. 8 we can easily find an initial SID of 81.2757 mmol/L and final SID of 162.8152 mmol/L with a difference of 81.5396 mmol/L; they are equal. Our approach easily allows consideration of a natural question: from where do charges involved come (Table 65.1)?

This shows that, by using this model, we can have an explicit account for the charges and thereby acid-base fluxes insofar as we are able to give a quantitative description of the situation under consideration.

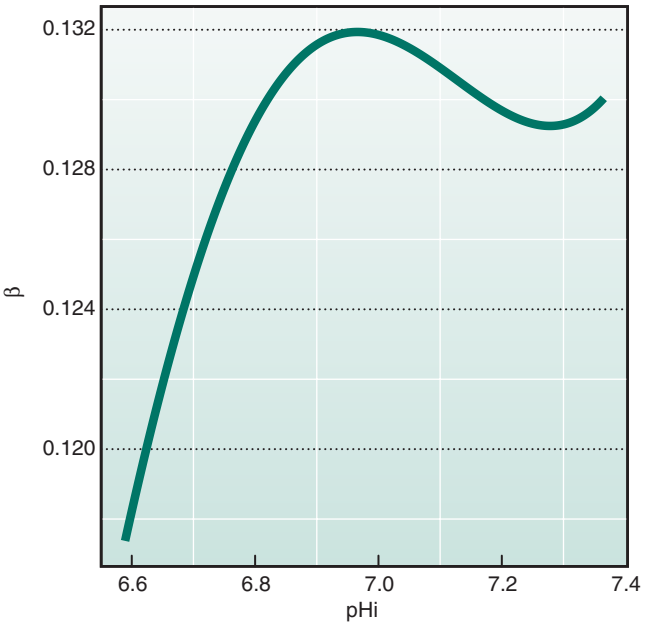

FIGURE 65.5 The buffer capacity calculated based on intracellular composition as described.

Buffering Based on Charge-Balance Modeling

The seminal work of Pitts and Alexander[26] provides another pointer to the analysis of acid-base with regard to the concept of buffering. Pitts and Alexander[26] interpreted their results in terms of buffer action. Therefore one dog had urine pH 6.43 and plasma pH 7.34 and excreted TA corresponding to 0.301 mmol/min H^+ at a gradient of 8:1 ~ $10^{-6.43}/10^{-7.34}$. In the absence of buffer, at a maximal gradient of 400 ($10^{-4.8}/10^{-7.4}$) only 6.4 mL/min × ($10^{-4.8}$-$10^{-7.4}$) mol/L ~ 0.1 μmol/min would be excreted, Pitts and Alexander concluded. Therefore, *under these fixed pH conditions*,

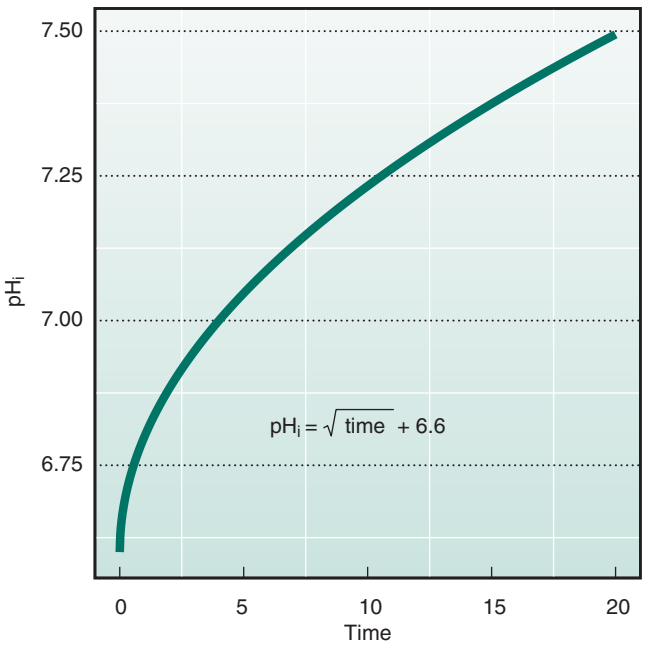

FIGURE 65.6 Recovery of pHi used to calculate proton flux as described in the text.

TABLE 65.1

Distribution of Charges

ΔSID	81.5396	
ΔHA		68.6724
ΔHCO_3^-		12.8357
ΔCO_3^{--}		0.03114
ΔOH^-		0.0001
ΔH^+		0.0002
sum		81.5396

HA, Undissociated weak acid; *SID,* strong ion difference.

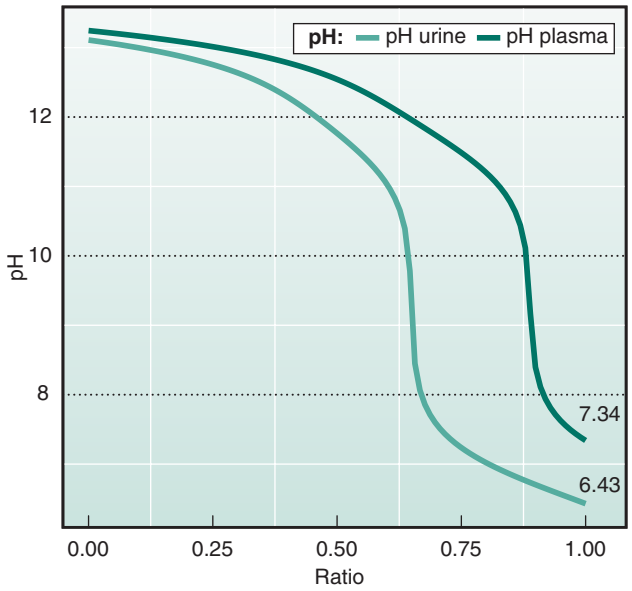

FIGURE 65.7 pH in urine and plasma as a urine P decreases, but SID in plasma and urine are kept constant, whereby titratable acidity is also constant. It is clear that reduced buffer does not hamper excretion of titratable acidity.

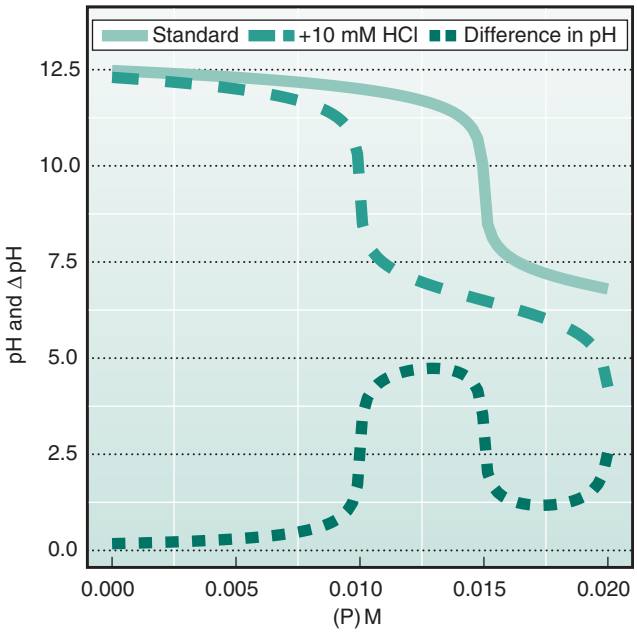

FIGURE 65.8 The effect on pH of increasing total phosphate from 0 to 20 mM when SID is kept constant at 30 mM *(solid line).* As 10 mM HCl is added, pH decreases *(dashed curve),* but not in a way that is a simple function of total phosphate concentration.

titratable acidity is a linear function of buffer concentration, and if there is no buffer, titratable acidity is zero.

However, in the definition of titratable acidity as provided from Henderson,[27] buffers are not mentioned, but the direct difference in strong ion differences are (strong bases-strong acids). To reproduce the SID values in plasma and urine as phosphate concentration is reduced from the initial value of 0.099 mol/L, pH can be calculated for urine and plasma. Here the range of pH values will be high, and for accurate results consideration of all three dissociations is necessary. According to Kildeberg,[30] charge on P as function of pH and [P] is

$$\frac{[P]*(10^{(pH-pK1)}+2*10^{(2*pH-pK1-pK2)}+3*10^{(3*pH-pK1-pK2-pK3)})}{(1+10^{(pH-pK1)}+10^{(2*pH-pK1-pK2)}+10^{(3*pH-pK1-pK2-pK3)})}$$

Employing this with the example dog of Pitts and Alexander[26] yields the information presented in Fig. 65.7.

Supplementary Note 3

When P is unchanged, ratio is 1, and, as measured by Pitts and Alexander, urine and plasma pH yield the measured titratable acidity of 0.302 mmol/min. When titratable acidity is kept constant (i.e., keeping SID in plasma and urine unchanged, while ratio is reduced to proportionally diminish P), pH in urine and plasma must increase. There is otherwise no problem in sustaining excretion of unchanged titratable acidity as P is reduced even to zero.

DuBose[14] described buffers as "systems that attenuate the pH changes in a solution or tissue by reversibly combing with and releasing H^+." To further understand the concept of buffering in a charge-balance discourse to see under which circumstances this perception of buffering is true, we can employ

$$[H^+]+SID-\frac{K_w}{[H^+]}-P*\left[1+\frac{K_a}{[H^+]+K_a}\right]=0$$

to specify a pure phosphate-buffered solution. Taking SID to be 30 mM and varying P between 0 and 20 mM produces the solid curve below (Fig. 65.8):

It is evident that the higher the buffer concentration, the lower pH is. Adding then HCl to the final concentration 10 mM yields the dashed curve in Fig. 65.8 (only very minimal difference results when looking at all three dissociations). Again it is not evident that a higher buffer concentration protects against decreasing pH as a result of the acid load. This is also evident when the change in pH is plotted against buffer concentration in the dotted curve in Fig. 65.8.

Therefore it is obvious that the effects of buffers are not straightforward but equally obvious that the employed algebra is useful in revealing the processes.

Buffering power, β, is dependent on prevailing pH in relation to pK of the buffer, so experiments to illustrate buffering could be done at fixed pH. To compare with the previous picture, initial pH was kept constant while P increased from 0 to 20 mM. This necessitates an increase in SID of 36 mM. Adding now 10 mM HCl *(dashed curve* in Fig. 65.9*)* gives a pH that increases with P and therefore a decline in pH *(dotted curve)* that is indeed dampened by the increased concentration of buffer (Fig. 65.9).

The analysis for the figures is presented in Supplementary note 4.

Supplementary Note 4

This is closer to the implicit understanding of buffering that usually is portrayed in acid-base physiology[14] but from a charge balance point of view, the underlying and necessary changes in strong ions is revealed here and typically disguised. Therefore the buffering shown in Fig. 65.9 is not only an effect of the P and pH but also of the SID required to fix the initial pH as wanted. This example again demonstrates that the charge balance–based notion

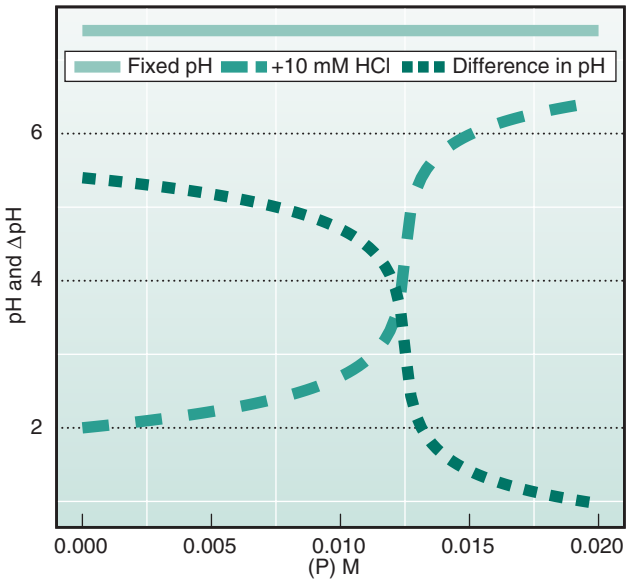

FIGURE 65.9 The effect on pH of increasing total phosphate concentration from 0 to 20 mM while keeping initial pH constant at 7.4 *(solid curve).* This necessitates increase in SID by 36 mM. Under these circumstances, adding 10 mM HCl causes a decrease in pH *(dashed line),* which is indeed much smaller *(dotted line)* as total phosphate increases.

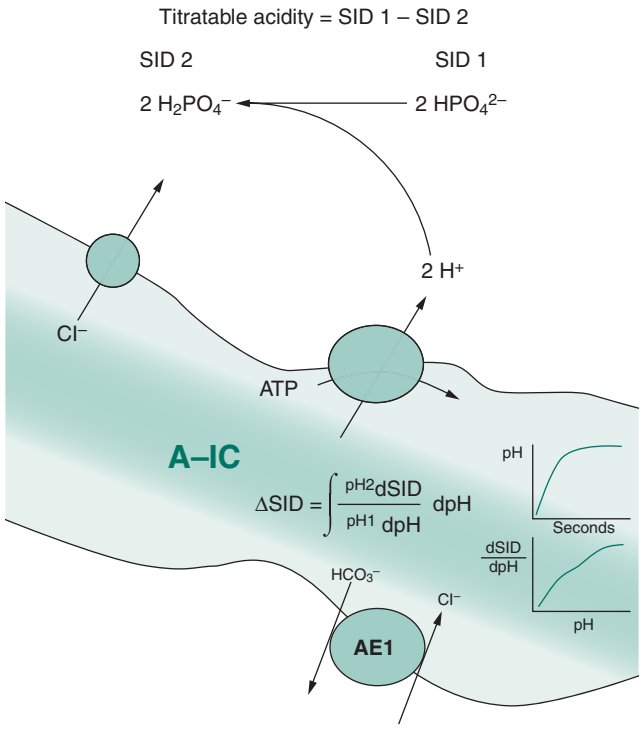

FIGURE 65.10 A model of a type A, acid secreting, intercalated cell from the collecting duct. It is illustrated how titratable acidity and proton secretion can be formulated in terms of SID constituents.

of acid-base makes possible explicit quantitative handling of these issues.

Plasma buffering is very dramatically enhanced by the open system provided by having pCO_2 controlled. Using Eq. 7 this is demonstrated also in Supplementary Note 4.

Finally, to show how the charge-balance notion of acid-base makes possible penetration of classical results, analysis of buffering as explained in Boron[31] is demonstrated in Supplementary Note 2a and 2b. To reiterate, in classic modeling flux of protons are formulated as

$$Flux = \int_{pH_1}^{pH_2} \frac{dSID}{dpH} dpH$$

which will simplify to ΔSID. Therefore, as shown in the example, instead of making assumptions or having difficult measurements of buffer capacity as pH changes and a series of pH measurements, we legitimately can calculate initial and final SID. This is an important simplification.

Modeling Renal Acid-Base Transports

A critical part of renal contribution to acid-base homeostasis occurs in the distal nephron.[2,3] A large number of transporters are involved in the regulation, and understanding how they individually and together contribute to regulation of acid-base is not straightforward by conventional means. Classical studies[19] show that proton secretion in the medulla depends heavily on concomitant Cl^- transport because of the electrogenic nature of H^+-ATPase. As shown above, measuring the proton flux by classical means already makes certain that measuring changes in strong ions will be aligned with the classical results in terms of individual transporters. The appealing feature of tallying in terms of strong ions is that the integrated response to a series of transports will be immediately available from urine measurements. AE1 or band 3 is involved in Cl^-/ HCO_3^- exchange in type A intercalated cells,[32] and dysfunction is a cause of distal renal tubular acidosis.

Fig. 65.10 presents the collecting duct with a type A intercalated cell. It is shown how the H-ATPase generates H^+ secretion, which can be examined as a shift in pH at a correspondingly measured buffer capacity,[4] whereby the connection with SID is fixed by definition. The secreted protons can be seen as generating titratable acidity, TA, which equivalently is the difference in SID, also as shown in the account of Pitts and Alexander.[26] Also the charge produced by the proton pump is neutralized in part by Cl^- conductance.[19,33] Likewise, the intracellular alkali generated is transported by the basolateral Cl^-/HCO_3^- exchanger AE1, for which the equivalence to transport of SID constituents is fixed a priori. It is reasonable to think of all the transporters thought to be involved in acid-base transports in terms similar to those shown in Fig. 65.10 and thereby to understand the entire acid-base functions of the kidney as consisting directly of transports of SID constituents.

In the conventional acid-base treatise, urinary NH_4^+ excretion is the most important instrument to increase renal net acid excretion (NAE) under acidosis, and very detailed accounts are indicative of the assigned importance.[34] Stewart opined that since there was very little NH_4^+ in plasma, its urinary excretion has no impact on acid-base homeostasis. It can be seen that if SID components are accounted for, NH_4^+ excretion must be ignored for a consistent assessment of acid-base balance.[35,36]

The project raised with the charge-balance paradigm of acid-base is to explore quantitatively the whole body model of acid-base regulation and first and foremost the roles of the kidneys. This is work in progress, and head-to-head comparison between the charge-balance and conventional model has not been published. However, a paper on a

model of distal renal tubular acidosis offers a view of what may be obtained,[37] and description and analysis is available in Supplementary note 5.

Supplementary Note 5

Briefly in that paper,[37] mice with knock out of distal Cl^-/HCO_3^- exchanger were said to have less urinary excretion of net acid compared with wild mice to explain the observed metabolic acidosis. Going through the numbers, however, the acidotic mice had greater acid excretion measured per time unit. However, the acidotic animals did excrete urine with a higher SID, which could explain their metabolic acidosis in contrast to conventional modeling.

Brown et al.[38] wrote in 1989:

> In analysis of acid-base balance, one must keep in mind the fact that electroneutrality dictates that the sum of the charges of the nonreactive ions in urine ($[Na^+]+[K^+]-[Cl^-]$) must be equal and opposite in signs to the sum of charges of buffer ions plus organic ions. Thus the contribution of urinary excretion to systemic acid-base balance can be assessed either by measuring the buffer plus organic ions or the nonreactive ions in urine.

A similar insight was demonstrated by Lemann et al.[39] reporting a strong effect whereby a negative whole body balance of $[Na^+]+[K^+]-[Cl^-]$ yielded a strongly positive acidifying effect.[39]

It has, in fact, been attempted to analyze individual transports in terms of the conventional acid-base paradigm (i.e., local NH_4^+ + titratable acidity [TA]).[40] However, the submitted deconstruction of this discourse[15] leaves little trust that this approach could be generalized, and as shown the conventional discourse contains duplication because NH_4^+ and TA are already interpretable as change in SID.

DIAGNOSING ACID-BASE DISORDERS

The plot (Fig. 65.11) shows the effects of changing four variables on pH as based on the charge-balance model. Eq. 7 allows answers to be obtained to any specific situation with regard to identified substances, which is an advantage compared with lumping together all weak acids, for instance. From this general point of view all acid-base disorders are mixed because, for their analysis, it is natural to scrutinize all known substances with impact on pH (i.e., everything with a charge, fixed or variable).

However, in clinical practice, acid-base disorders are handled initially based on a sample of arterial blood. The spider plot shows how percentage change of SID, pCO_2, albumin, and phosphate from their central values of 35 mM, 40 mmHg, 40 g/L, and 1 mM, respectively, influences pH; it is evident that SID and pCO_2 have a major impact. Accordingly, it is natural to organize the presentation of acid-base disorders along two dimensions, metabolic and respiratory, in the first approximation.

A huge material of observations helps the partition of states into acute and chronic disorders according to commonly observed responses, whereby in primary respiratory disorders, metabolic compensations are observed and in primary metabolic disorders, a compensatory respiratory response takes place. The detailed mechanisms whereby these compensations are elicited and organized are not understood, because this understanding requires the integrated whole-body acid-base model, which is not yet in place. Giebisch and Pitts[41] described extrarenal

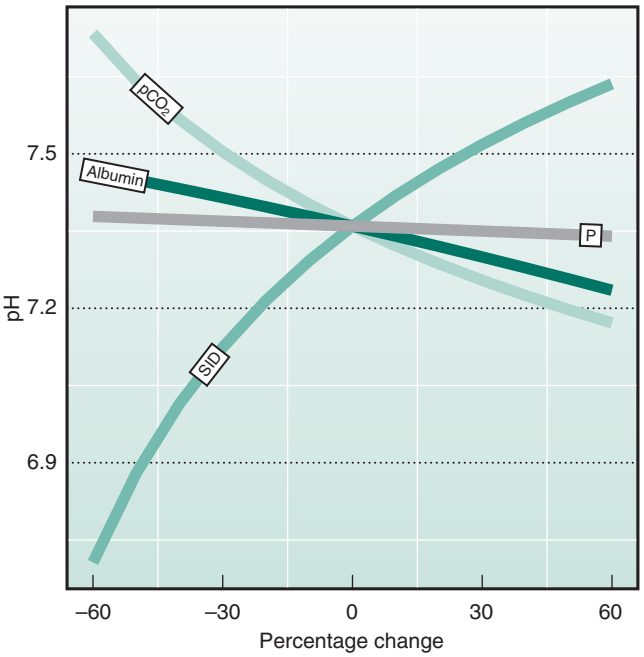

FIGURE 65.11 Spider plot showing the effect on pH of varying each of SID, pCO_2, albumin, or phosphate from normal mean values while keeping the other variables at mean values. The effect of SID and pCO_2 are seen to be dominant.

compensations to respiratory acid-base disorders, and these included a series of transports of strong ion constituents and also changed weak acid distributions. Focusing on the spider-plot (Fig. 65.11), it may be surmised that the most important compensations occur along the dimensions of SID and pCO_2, but to understand the changes in SID requires accounting for the constituents of SID, mainly Na^+ and Cl^-. Consequently, accounting for the effect of SID on acid-base requires understanding of the individual components. Some progress has been made with regard to Na^+,[42] but major problems remain in explaining Cl^-. It is distributed mainly in the extracellular fluid,[43] but its apparent volume of distribution may change, for instance, in sepsis.[44] Chloride is involved in the metabolic compensation to respiratory acidosis,[45] and a number of renal Cl channels and transporters are involved in diseases related to acid-base.[2] One important general theme in acid-base physiology with a focus on chloride has been the role in maintaining metabolic alkalosis. In a number of experimental models comprising volume and chloride depletion, a common interpretation is that repair is obtained solely by repleting chloride also without restoring volume deficit.[46] From a charge-balance point of view this must be only partially true. Just as dilution acidosis is a direct fact that can be observed in practice and deduced from the physical chemistry,[47] alkalosis is an inevitable consequence if pCO_2 is maintained while SID, albumin, and P are all increased as water is lost. The code available in Supplementary Note 6 demonstrates the utility of a formal charge-balance model in demonstrating this fact.

Supplementary Note 6

Therefore, even if a decreasing Cl^- obviously will increase SID and thereby pH, and correcting chloride depletion will

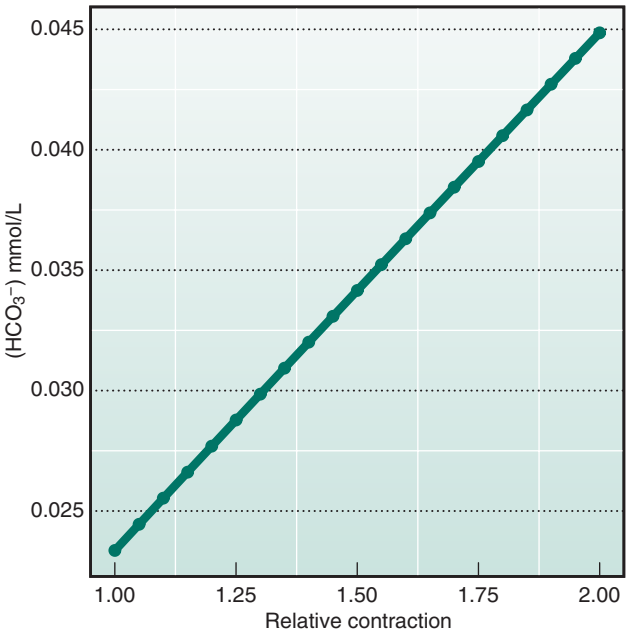

FIGURE 65.12 Simulated contraction alkalosis. It is assumed that pCO_2 is kept constant at 40 mm Hg, while SID, phosphate, and albumin increase in proportion to the contraction.

ameliorate this effect,[48] this does not prove that contraction alkalosis does not exist (Fig. 65.12). To evaluate the importance of chloride together with other factors affecting the regulation of pH requires a model that is able to put these variables together in an explicit expression. The charge-balance model alone has this depth. This obviously does not in any way diminish the importance of the detailed accounting for Cl^- transporters in the kidney and elsewhere,[2,49] but describing together a series of such transporters represents no integrated biologic model.

One particularly difficult theme in acid-base physiology is integrating the many organs and compartments in a whole-body construct. Acid-base normally is analyzed with a focus on arterial blood samples, but this is not necessarily representative of intracellular processes.

Jones[50] examined the acid-base response to prolonged dietary potassium depletion in normal persons. It was evident that a slight metabolic alkalosis developed, yet NAE (although assessed, of course, by classical means) decreased during induction and also maintenance.[51] The interpretation was that intracellular potassium depletion resulted in intracellular acidosis. As a corollary, potassium in urine, which quantitatively may equal sodium, cannot be referred to the plasma compartment. Therefore strong ion difference in the urine may be a useful measure with regard to total body acid-base homeostasis rather than merely plasma acid-base homeostasis.[52] A corollary of this discussion is that the clinical impact of acidosis may be dependent on the actual mechanism (i.e., acidosis with a high Cl^- may have a more grave prognosis).[53]

Finally, with regard to the intra- and extracellular homeostasis and equilibrium, we reported that in salicylate intoxication, a significant gap between end expiratory and arterial blood pCO_2 developed that was higher as salicylate increased.[54] The finding was explained in referring to Wieth and Brahm,[55] who showed that salicylate-induced hyperventilation was maintained when dogs were infused with salicylate-treated blood in spite of washing the free salicylate away and also showed that salicylate inhibited band 3: Cl/HCO_3^- exchanger in the red blood cells. A corollary was that in spite of the arterial blood with normal or low pCO_2, a tissue respiratory acidosis developed to explain the well-known fact that it may be difficult get alkaline urine to enhance salicylate excretion. One more corollary could be that in anemia, dissociation develops between tissue and arterial blood pCO_2. This is not excluded by the finding that net CO_2 transport is maintained in anemia[56] as it axiomatically should be for survival, and peripheral CO_2 transport is not necessarily only simple diffusion.[57] There is more quantitative work needed in this area, and the charge-balance discourse is well prepared for that.

PRACTICAL APPROACH

1. The first thing to do is to compare measured pH to calculated pH according to a formula like Eq. 7 and modified according to the actual situation if necessary. This serves several purposes: forcing one to ensure measurements were properly taken and recorded and forcing one from the beginning to see if a complex disorder is present. This often requires measurement of Na, K, Ca, Mg, Cl, albumin, phosphate, lactate, pCO_2, and frequently entails supplementary measurement of salicylate and beta-hydroxybutyrate. At the same time, it may be prudent to calculate an osmolal gap, as stated below. With these steps completed, clinicians are unlikely to miss important problems with unmeasured moieties, although subtle problems with measurements may remain[58] (e.g., dramatic overmeasurement of chloride in the presence of high salicylate).
2. Is there an evident acid-base disorder (pH is abnormal) such as alkalosis or acidosis?
3. Calculate expected compensations according to a primary disorder according to the table below:

Rules for Predicting Appropriate Acid-Base Compensation

Disorder	HCO_3^- mmol/L	pCO_2 mm Hg
Metabolic acidosis	<22	$1.5 * HCO_3^- + 8$
Metabolic alkalosis	>26	$0.7 * HCO_3^- + 20$
Respiratory acidosis		>45
Acute	$24 + \frac{PaCO_2 - 40}{10}$	
Chronic	$24 + 4 * \frac{PaCO_2 - 40}{10}$	
Respiratory alkalosis		<35
Acute	$24 - 2 * \frac{40 - PaCO_2}{10}$	
Chronic	$24 - 5 * \frac{40 - PaCO_2}{10}$	

4. Calculate expected gaps, including a strong ion gap (SIG) according to Eq. 7 or equivalently from the formulae in the table below, and including osmolal gap.

5. Compare the SIG to standard base excess. The gaps are calculated as stated[59] below in the table:

Gap	Calculation	Reference Range
Anion gap (AG)	$[Na^+]+[K^+]-[Cl^-]-[HCO_3^-]$	7-17 mEq/l
Albumin-adjusted anion gap	$AG+0.25*(40-Alb)$	7-17 mEq/l
Corrected anion gap (AG_c)	$AG-(0.2*Alb+1.5*[P])$	< 5 mEq/l
Strong ion gap (SIG)	$[Na^+]+[K^+]+2*[Mg^{2+}]+2*[Ca^{2+}]-[Cl^-]-[HCO_3^-]-[_LLactat^-]-Alb*(0.123*pH-0.631)-[P]*(0.309*pH-0.469)-0.0301*pCO_2*10^{pH-6.1}$	< 5 mEq/l
Osmolal gap	$2*[Na^+]+glucose+urea+1.25*ethanol$[60]	< 10 mosm/kg

It must be understood in the light of the completely explicit charge-balance model that the gaps are shorthand with shortcomings.[61,62] At the same time, however, the observed gaps in various circumstances represent a valuable basis of common experience that we should not sacrifice at present.

Application of Strong Ion Analysis

Are the kidneys causing or compensating the disorder? How can strong ion analysis be applied? When acid-base disorders are analyzed using the customary means as described, the best result is a correct classification of the state, which frequently can be recognized as a well understood clinical entity. This is certainly useful, but it also would be of interest to develop a more quantitative assessment to be able to answer questions about the specific origin of the acid-base disorder and the compensation observed. A common approach in nephrology is to organize disorders into those that are caused by renal mechanisms as compared with those ameliorated by renal compensations.

Obviously this assessment first requires that we have a solid way of quantifying renal acid excretion, which NAE does not deliver.[15,16,63] Therefore, as an example, even though we know much of detail in the molecular pathophysiology of renal tubular acidosis,[64] whether in renal tubular acidosis (RTA), NAE is increased or not is not known.[37,65] Also, when endogenous acid production, which may be influenced by acidosis,[66,67] and food intake of alkali are not accounted for, it is difficult to determine what is expected.

In contrast, employing a charge-balance approach, Moviat et al.[68] studied critically ill patients with impaired renal function and found the urinary excretion of Na^+-Cl^- to be higher in the more acidotic, indicating that the metabolic acidosis was at least in part mediated by renal mechanisms. As previously described, this may be a starting point in organizing understanding the renal function in acid-base.[69] Likewise, the effect of acetazolamide in correcting the metabolic alkalosis was well explained by increasing sodium relative to chloride in urine, thereby decreasing plasma SID and pH,[70] again similar to the results from Lemann[39] in 1965.

Fundamental Critique of Charge-Balance Construct

The notion that charge-balance provides a useful fundament for understanding acid-base, although derived from incontrovertible physical chemistry[5-7] and validated in clinical practice,[22] is not without its opponents. Particularly influential has been a review by Kurtz et al.[71] A rebuttal is available in supplementary materials.

Supplementary Note 7

A broader discussion of these issues is found in reference 22. Supplementary notes are available from https://figshare.com/articles/Critical_care_nephrology_chapter_65_Acid–Base_physiology/4231364/1.

Key Points

1. Employing the strong requirement of charge-balance to understand acid-base yields a model that has been clinically validated.
2. The charge-balance model allows understanding buffering in terms of strong ion difference. This makes possible the interpretation of acid-base transport in terms of strong ions.
3. The charge-balance model approaches all acid-base disorders as mixed by examining the contribution of every measurement to charge-balance. Here, focus is naturally on the underlying mechanisms.

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A complete reference list can be found online at ExpertConsult.com.

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