

[PART II]

**QUANTITATIVE ACID-BASE
CHEMISTRY AND PHYSIOLOGY**

[CHAPTER 10]

Normal [SID]

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10.1 INTRODUCTION

This chapter will discuss issues surrounding the measurement and conceptualization of a “normal” strong ion difference (SID). Recall from Chapter 4 that [SID] is defined as the charge difference between the sum of all strong cations and the sum of all strong anions. Although this would seem to be straightforward, there are a number of matters of physical chemistry and physiology that complicate our understanding of normal [SID]. It is important to gain some insight into these concepts because how normal is defined establishes a point of reference by which abnormal (disease) is measured.

10.2 PHYSICAL CHEMISTRY OF NORMAL SID - MEASUREMENT

As a first approximation, [SID] of plasma can be calculated from the net charge of $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$. If one were to take blood samples from 100 healthy medical students at rest, plasma [SID] might be calculated to be:

$$[\text{Na}^+] (140 \text{ mEq/L}) + [\text{K}^+] (4 \text{ mEq/L}) - [\text{Cl}^-] (100 \text{ mEq/L}) = 44 \text{ mEq/L}$$

This simple example illustrates that although [SID] is easily defined, it must be calculated from the measure of its constituents. Obviously in our sample of 100 healthy resting medical students there will be variation in these concentrations resulting from normal variation for each ion between individuals, and from laboratory variation in measurement within any one individual. Thus, rather than speaking of a normal [SID], it is probably more accurate to refer to a normal range for [SID].

The normal range for $[\text{Na}^+]$ is 135-145 mEq/L, for $[\text{K}^+]$ is 3.5-4.5 mEq/L and for $[\text{Cl}^-]$ is 95-105 mEq/L. With respect to variability in laboratory measurement, the coefficients of variation for $[\text{Na}^+]$, $[\text{K}^+]$ and $[\text{Cl}^-]$ are 1.0%, 3.5% and 1.5% respectively, and the standard deviation for repeated measures of [SID] can be calculated to be 1.8 mEq/L [1]. From the normal range of $[\text{Na}^+]$, $[\text{K}^+]$ and $[\text{Cl}^-]$ the theoretical extremes of normal SID are 54.5 to 33.5 mEq/L (Table 10.1).

Condition 1	Condition 2
[Na ⁺] = 145.0 mEq/L	[Na ⁺] = 135.0 mEq/L
[K ⁺] = 4.5 mEq/L	[K ⁺] = 3.5 mEq/L
[Cl ⁻] = 95.0 mEq/L	[Cl ⁻] = 105 mEq/L
SID = 54.5 ± 1.8 mEq/L	SID = 33.5 ± 1.8 mEq/L

Table 10.1. Conditions 1 and 2 demonstrate the theoretical range of normal SID based on the accepted normal values for [Na⁺], [K⁺] and [Cl⁻].

Given standard values for PCO₂ of 40 mmHg and total weak acid concentration ([A_{TOT}]) of 20 mM, this range of [SID] would result in pH values of 7.54 ([HCO₃⁻] = 35.8 mM) to 7.2 ([HCO₃⁻] = 16.2 mM) respectively. From a clinical assessment point of view, this range of “normal” SID is at best too broad to be very informative and at worst, clinically misleading. Fortunately, homeostatic mechanisms function to maintain SID within a narrower range. Gunner-son et al [2] demonstrated that [SID] in healthy volunteers was 40±3.8 mEq/L and Kellum [3] reported [SID] in the range of 40 to 42 mEq/L, also in healthy volunteers.

The above example is based on [SID] being measured as [Na⁺] + [K⁺] – [Cl⁻], when in fact [SID] is defined as the net charge difference between the sum of all strong cations and all strong anions. Thus, [Ca²⁺] and [Mg²⁺] and all strong organic acids such as lactate, sulphate, ketoacids, etc. should be included in the calculation, especially at the extremes of physiological pH [4]. The more of the constituents of [SID] that are measured, the closer the calculation should be to the true value. Currently, [SID] is routinely measured from [Na⁺] + [K⁺] + [Ca²⁺] + [Mg²⁺] – [Cl⁻] – [Lac⁻] [2, 3, 5, 6]. The addition of divalent cations and lactate in the measure of [SID] almost cancel each other in healthy individuals and so do not appreciably change the expected normal value in this population. However, these strong ions, especially lactate, can be significantly altered in disease states, and should thus be included in the calculation.

There are two other methods by which [SID] can be calculated or perhaps we should say, “estimated”. From the law of electrical neutrality, closely approximated by:

$$[\text{SID}] - [\text{HCO}_3^-] - [\text{Alb}^-] - [\text{Phos}^-] = 0 \quad (10.2.1)$$

where [SID] = [Na⁺] + [K⁺] + [Ca²⁺] + [Mg²⁺] – [Cl⁻] – [Lact⁻], it can be seen that it is equally valid to estimate [SID] as the sum of all weak anions [7]:

$$[\text{SID}] = [\text{HCO}_3^-] + [\text{Alb}^-] + [\text{Phos}^-] \quad (10.2.2)$$

The law of electrical neutrality states that [SID] calculated from either strong electrolytes measured directly or Equation (10.2.2) must be equal. If they are not, then there is either measurement error and/or not all electrolytes are being accounted for. As shown in Figure 10.1, if measured electrical neutrality (from SID ([Na⁺] + [K⁺] – [Cl⁻] – [Lact⁻]) – [HCO₃⁻] – [dissoci-

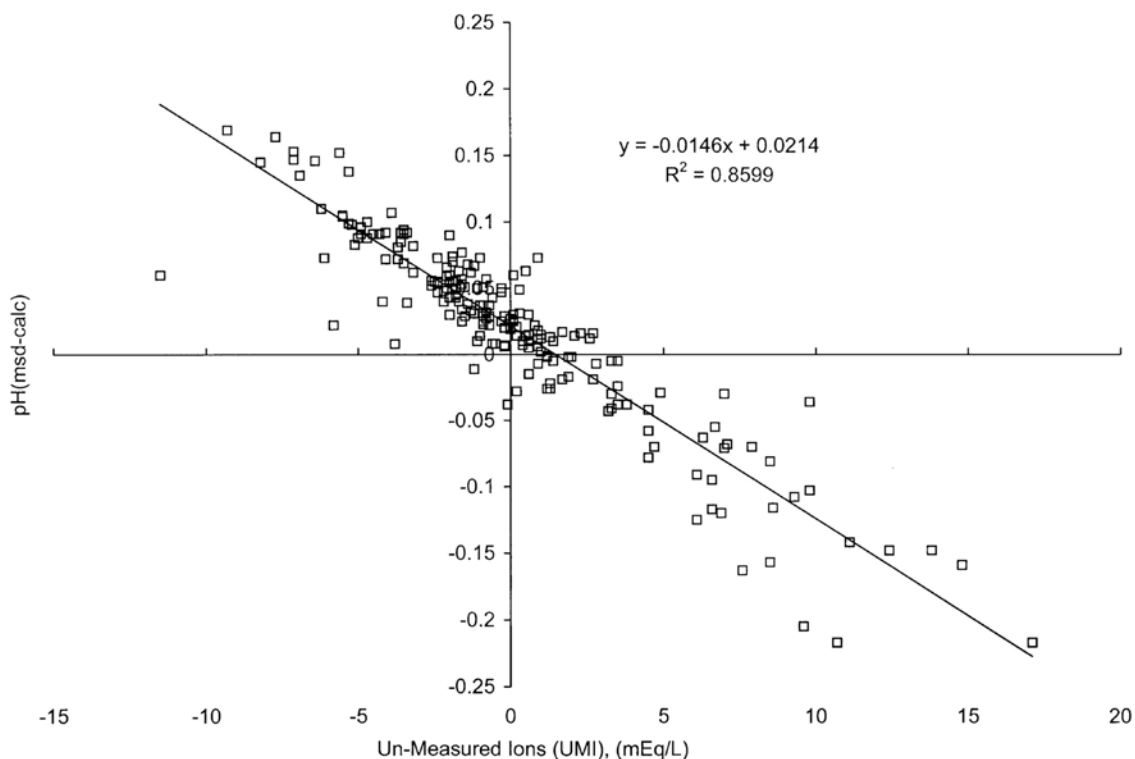


Figure 10.1. This figure demonstrates a linear relationship between calculation of electrical neutrality and the accuracy of the resulting calculation of pH (data from [12])

ated weak acid)) is greater than zero then calculated pH exceeds measured pH. Conversely, if measured [SID] is less than zero, then calculated pH is less than measured pH. However, if the measured electrolytes actually do add up to electrical neutrality then the difference between measured and calculated pH is only 0.0214. Although electrical neutrality always exists, Figure 10.1 illustrates the technical difficulties in actually measuring it.

10.3 PHYSICAL CHEMISTRY OF NORMAL [SID] – CONCENTRATION VS. ACTIVITY

The final method of determining [SID] is based on the inviolate law of electrical neutrality that acts as a powerful physical and conceptual constraint on the system. In a landmark study by Figge et al. [6], [SID] calculated from direct measurement of strong ions is termed an apparent [SID] ([SID]_A), while that [SID] calculated to account for electrical neutrality is viewed as the effective [SID] ([SID]_E). The difference between [SID]_A and [SID]_E is termed the strong ion gap ([SIG]) [8], and is due, in part, to the presence of unmeasured organic anions, likely Krebs' cycle intermediates [9, 10].

The clinical significance of [SIG] will be discussed Chapter 18, but it is raised here because

[SIG] may also be explained, in part, by the difference between ionic molar concentration and ionic activity. Ionic molar concentration is a measure of the actual number of ions in solution. In contrast, ionic activity is a measure of the effective concentration of electrolytes that results from the charge interaction on dissociated species. The difference between ionic concentration and ionic activity is important because the molar concentration of any electrolyte will not affect the molar concentration of any other electrolyte, but ionic activities are mutually interactive; and, the law of electrical neutrality only refers to the latter [11].

Thus, with respect to ionic activity, strong ions and weak electrolytes should probably not be viewed as being fully independent variables. To illustrate how this concept may impact on our understanding of normal [SID], it is frequently pointed out that the pH of normal saline is 5.5 even though the concentrations of $[\text{Na}^+]$ and $[\text{Cl}^-]$ are both 154 mEq/L and therefore [SID] is zero. Accordingly, the pH of normal saline should be equivalent to water ($\text{pH} = 7$ at 25°C). The explanation for this discrepancy between measured and expected results is as follows. Normal saline is a 0.9% solution of completely dissociated NaCl. However, it is also an aqueous mixture of equal parts HCl and NaOH. Since HCl is a stronger acid than NaOH is a base, the affinity of $[\text{Na}^+]$ for $[\text{OH}^-]$ is greater than the affinity of $[\text{Cl}^-]$ for $[\text{H}^+]$. Note the difference between the strength of an acid or base, which refers to the magnitude of the dissociation constant, and its concentration. These differences in strength result in a slight excess of $[\text{H}^+]$ in solution, and hence a lower pH. Thus while the $[\text{SID}_A]$ is zero, there is an $[\text{SID}_E]$ which can be thought of as the [SID] needed to account for the measured $[\text{H}^+]$. The $[\text{SID}_E]$ in this simple system is readily calculated from the mathematical solution of NaCl and water. Given that $[\text{SID}] = [\text{Na}^+] - [\text{Cl}^-]$ in a saline solution, the mathematical solution is the law of electrical neutrality and dissociation of water:

$$\text{Statement of electrical neutrality: } [\text{SID}] + [\text{H}^+] - [\text{OH}^-] = 0$$

$$\text{Dissociation of water: } [\text{H}^+] \times [\text{OH}^-] = K'_w$$

where K'_w is the dissociation constant for water. Re-expressing $[\text{OH}^-]$ in terms of K'_w and $[\text{H}^+]$ gives

$$[\text{OH}^-] = \frac{K'_w}{[\text{H}^+]}$$

substituting $K'_w/[\text{H}^+]$ for $[\text{OH}^-]$, and re-arranging terms yield:

$$\text{SID} = \frac{K'_w}{[\text{H}^+]} - [\text{H}^+] \quad (10.3.1)$$

Since $K'_w = 4.4 \times 10^{-14}$ (at 25°C) and $[\text{H}^+] = 3.16 \times 10^{-6}$ Eq/L (from $\text{pH} = 5.5$), the $[\text{SID}_E]$

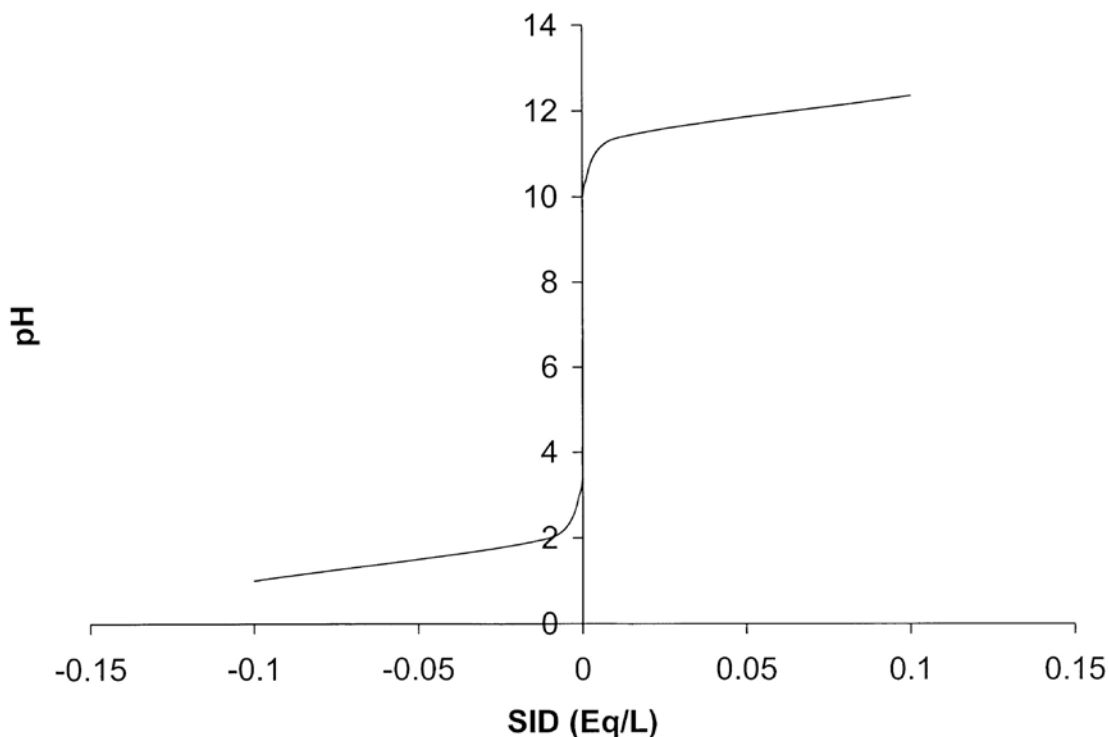


Figure 10.2. pH titration curve for saline at 25 °C.

$= -3.1 \times 10^{-6}$ Eq/L. The reason why [SID] of such a small magnitude has such a pronounced influence on pH is that the inflection point of the titration curve for saline is extremely sharp around pH 7 (Figure 10.2), i.e. saline is poorly buffered. Generally speaking, the practical (clinically significant) difference between measured ionic concentration and ionic activity can be ignored. However, as stated by Stewart (see Chapter 2), the distinction between measured concentration and effective concentration is always “lurking in the background”. It should be carefully examined whenever disparities arise between simple theory and the results of careful measurements.

These then are some of the issues of physical chemistry that influence our understanding of normal [SID]. To summarize to this point: [SID] of a single compartment aqueous system (plasma) is always defined as the net charge difference between the sum of all strong cations and all strong anions (both inorganic and organic), but, assigning an actual number or range for normal [SID] is affected by the number of strong ions that are measured, the method of measurement (activity vs. concentration) and, the accuracy by which they can be measured.

10.4 PHYSIOLOGY OF NORMAL SID – CO-DEPENDENCY OF [SID], PCO_2 AND $[\text{A}_{\text{TOT}}]$

In addition to issues of physical chemistry, there are issues of physiology that influence our understanding of normal [SID]. For example, given that [SID] is approximately 40-44 mEq/L in healthy volunteers, and given that the population of healthy volunteers is not the patient population of most interest with respect to electrolyte/acid-base status, it is prudent to understand what is normal for the population of concern [5]. In the study by Gunnerson et al [2] mentioned above, the [SID] of stable ICU patients was 33 ± 5.6 mEq/L, and in a study by Wilkes [12] it was found that [SID] of ICU patients, calculated from $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{Lactate}^-]$ (where the greatest lactate was only 2.5 mEq/L) was 38.2 ± 4.1 mEq/L. Conversely, Story et al. [5] reported an [SID] of 46 mEq/L in a population of stable ICU patients. Thus, while there is perhaps no consensus as to what is normal for an ICU population, there is evidence to suggest it may not be 40-44 mEq/L as found in a non-ICU population. These alternate values of [SID] found in ICU patient populations raise some interesting questions, and possibly concerns.

Given that the ICU patient populations in the above studies were relatively stable, i.e. not in florid septic shock, it should be asked if the observed [SID] is 1. the response of electrolyte homeostatic mechanisms responding appropriately to an altered physiological state of chronic illness and thus, is an expected normal for this patient population, 2. a primary pathophysiological abnormality in electrolyte homeostatic mechanisms, perhaps to which therapy should be directed, or 3. an iatrogenic result given that intravenous fluid administration and enteric tube feeding is a standard part of care of most ICU patients? Although by no means mutually exclusive, it is important to ask these three questions when evaluating the electrolyte/acid-base status of an individual patient in the ICU in that the answer will influence both diagnosis and treatment.

Since the focus of this chapter is to understand normal [SID], the following discussion will be limited to the first question raised above, which as stated, is perhaps somewhat nebulous. What exactly do we mean by a normal physiological response to chronic illness? The conceptual issue in need of discussion pertaining to understanding normal SID is that there is a degree of co-dependency between [SID], PCO_2 and $[\text{A}_{\text{TOT}}]$ that exists when the system definition expands from a single aqueous compartment to multi-compartmented whole body physiology. In this more complex system [SID] is 40-44 mEq/L in part, because PCO_2 is 40 mmHg and $[\text{A}_{\text{TOT}}]$ is 14-20 mM.

A corollary of this statement is that an [SID] of 40-44 mEq/L would be abnormal if either $[\text{A}_{\text{TOT}}]$ or PCO_2 were altered. The concept of co-dependency between [SID], PCO_2 and $[\text{A}_{\text{TOT}}]$ may at first appear to be in direct conflict with the physicochemical approach to acid-base. In the original solution to $[\text{H}^+]$ in plasma as developed by Stewart, a fundamental principle was that in a system defined as a single compartment aqueous solution (plasma) there are a total of 9 variables ($[\text{SID}]$, PCO_2 , $[\text{A}_{\text{TOT}}]$, $[\text{H}^+]$, $[\text{OH}^-]$, $[\text{HCO}_3^-]$, $[\text{CO}_3^{2-}]$, $[\text{A}^-]$, $[\text{AH}]$). What makes the chemistry and mathematics manageable are that 1. the system is defined as a single compartment, 2. the electrolytes and gases are in steady state, and 3. three of the nine variables, ($[\text{SID}]$, PCO_2 and $[\text{A}_{\text{TOT}}]$), are independent. Accordingly, the system can be solved numerically with six

equations.

An independent variable is defined as one that influences the system, but is not influenced by the system. How [SID], PCO_2 and $[\text{A}_{\text{TOT}}]$ are independent variables can be illustrated with the following in vitro example. If one were to take a 1 l beaker of water (a single compartment system) and equilibrate it to $\text{PCO}_2 = 40$ mmHg and then add 20 mmol of plasma weak acids (80 g), $[\text{A}_{\text{TOT}}]$ would be 20 mM but PCO_2 will not be affected. If we were to then add 140 mEq of NaOH and 100 mEq of HCl the solution would have 140 mEq/L of $[\text{Na}^+]$ and 100 mEq/L of $[\text{Cl}^-]$, an [SID] of 40 mEq/L and again neither PCO_2 nor $[\text{A}_{\text{TOT}}]$ would be altered. Physiologically, PCO_2 is a function of the rate of PCO_2 production and alveolar ventilation, $[\text{A}_{\text{TOT}}]$ is a function of the rates of weak acid anabolism and catabolism and the volume of distribution, and [SID] is a function of rates of intake and loss, and volumes of distribution of each of its constituents, thus [SID], PCO_2 and $[\text{A}_{\text{TOT}}]$ would appear to fulfill the criteria for being independent variables.

Although the definition of an independent variable does not change, the status of a given variable as being independent or dependent is a function of how the system is defined. This can also be illustrated in vitro with the well-known Donnan equilibrium system. Briefly, Donnan equilibrium describes a system containing two saline compartments - (i) and (o) - separated by a semi permeable membrane. Both compartments contain $[\text{Na}^+]$ and $[\text{Cl}^-]$ (and of course $[\text{H}^+]$ and $[\text{OH}^-]$) that can cross the membrane. However, compartment (i) contains weak, dissociated proteins ($[\text{Prot}^-]$) that cannot cross the membrane (Figure 10.3). The numerical description of this system (from unpublished lecture notes of Dr. Stewart) is described by 11 equations and three independent variables (Table 10.2). It can be seen that the presence of $[\text{Pro}^-]$ in compartment (i) forces [SID] to be different on the two sides of the membrane in order to maintain Donnan equilibrium. Accordingly, [SID] in either compartment is determined from within the system and is therefore not an independent variable. However, the total amount (not concentration) of sodium (Na_{TOT}) and chloride (Cl_{TOT}) in both compartments, as well as the total amount of protein (P_{TOT}), are independent variables. Regardless of the [SID] in either compartment, Na_{TOT} and Cl_{TOT} (and P_{TOT}) will not change. As is well known, the final concentration of $[\text{Na}^+]$ and $[\text{Cl}^-]$ in both compartments is described by the Nernst equation:

$$\Delta P = \frac{RT}{zF} \times \log \frac{C_i}{C_o}$$

Such that

$$\Delta P = 61 \times \log \frac{[\text{Na}^+]_i}{[\text{Na}^+]_o} = 61 \times \log \frac{[\text{Cl}^-]_o}{[\text{Cl}^-]_i}$$

The ratio $[\text{Na}^+]_i/[\text{Na}^+]_o = [\text{Cl}^-]_o/[\text{Cl}^-]_i$ is called the Donnan ratio and equals 1.04.

The $[\text{H}^+]$ in either compartment is still determined by the SID (and protein concentra-

$$[\text{Na}^+]_o - [\text{Cl}^-]_o + [\text{H}^+]_o - [\text{OH}^-]_o = 0$$

$$[\text{Na}^+]_i - [\text{Cl}^-]_i + [\text{H}^+]_i - [\text{OH}^-]_i - [\text{Prot}^-]_i = 0$$

$$[\text{Na}^+]_i + [\text{Na}^+]_o = \text{Na}_{\text{TOT}}$$

$$[\text{Cl}^-]_i + [\text{Cl}^-]_o = \text{Cl}_{\text{TOT}}$$

$$[\text{Prot}^-] + [\text{HP}] = \text{P}_{\text{TOT}}$$

$$[\text{H}^+]_i \times [\text{Prot}^-] = K_p \times \text{HP}$$

$$[\text{H}^+]_i \times [\text{OH}^-]_i = K'_w$$

$$[\text{H}^+]_o \times [\text{OH}^-]_o = K'_w$$

$$[\text{Na}^+]_i \times [\text{Cl}^-]_i = [\text{Na}^+]_o \times [\text{Cl}^-]_o$$

$$[\text{H}^+]_i \times [\text{Cl}^-]_i = [\text{H}^+]_o \times [\text{Cl}^-]_o$$

$$\Delta P = RT \times$$

$$([\text{Na}^+]_i + [\text{Cl}^-]_i + \text{P}_{\text{TOT}} + [\text{H}^+]_i + [\text{OH}^-]_i - [\text{Na}^+]_o - [\text{Cl}^-]_o - [\text{H}^+]_o - [\text{OH}^-]_o)$$

Table 10.2. The distribution of electrolytes across the semipermeable membrane in the Donnan Equilibrium are described by 11 equations (Stewart, unpublished). K_p is the dissociation constant for proteins, K'_w is the dissociation constant for water, and R and T represent the universal gas constant and temperature respectively.

tion) of that compartment. The fact that the membrane is permeable to $[\text{H}^+]$ (and $[\text{OH}^-]$) is not conceptually or quantitatively important to the final $[\text{H}^+]$ of the solution on either side of the membrane.

Although chloride distribution between plasma and red blood cells is closely approximated

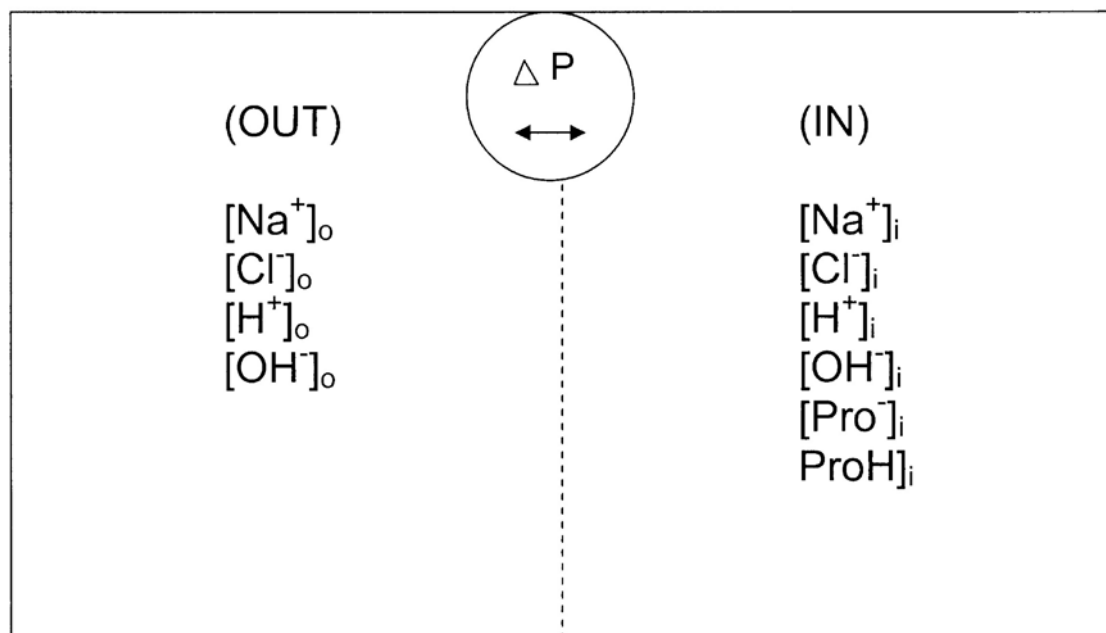


Figure 10.3. A schematic representation of Donnan equilibrium. $[\text{Na}^+]$, $[\text{Cl}^-]$, $[\text{H}^+]$, $[\text{OH}^-]$ are found in both compartments, and are able to move freely across the semipermeable membrane (dotted line). However, dissociated ($[\text{Pro}^-]$) and undissociated ($[\text{ProH}]$) protein are restricted by the membrane to compartment (i). ΔP represents the electrical potential (voltage) that is established across the membrane.

by a Donnan equilibrium [13], Donnan forces fall short of explaining the distribution of electrolytes between most other two-compartment physiological systems. For example, 26 equations and 10 independent variables are necessary to fully describe the influence of electrochemical, hydrostatic and osmotic gradients that ultimately determine the electrolyte concentration and volume differences between the interstitial and plasma compartments. The point of going through this exercise is not to solve these equations, but to set the stage for a discussion of how normal [SID] is affected by change in PCO_2 and $[\text{A}_{\text{TOT}}]$ in whole body physiology.

10.5 PHYSIOLOGY OF NORMAL [SID] – COMPENSATORY RESPONSES

Plasma electrolyte concentrations, and therefore [SID], are in part determined by dietary salt intake. As shown in animal studies, [SID] will vary inversely with dietary salt intake [14, 15]. The decrease in [SID] during high salt intake resulted from a greater increase in $[\text{Cl}^-]$ than $[\text{Na}^+]$. However, water intake in these studies was maintained constant, and as shown by Cowley et al. [16], when allowed ad libitum water intake, animals were able to regulate plasma electrolytes more closely. Similarly, patients who are transfused large volumes of normal saline

will increase their $[\text{Cl}^-]$ much more than $[\text{Na}^+]$, subsequently lowering $[\text{SID}]$ [17]. Accordingly, iatrogenic changes in $[\text{SID}]$ during fluid resuscitation should probably be viewed as an imbalance between salt and water intake, rather than representing a physiologically normal change of state. The importance of adequate free water intake to achieving appropriate electrolyte status is probably underestimated in ICU patients.

10.6 ACID-BASE DISTURBANCES

The traditional approach to acid-base physiology describes how primary respiratory and metabolic disturbances compensate each other. Briefly, respiratory acidosis and alkalosis are said to be respectively compensated by a renally mediated increase and decrease in $[\text{HCO}_3^-]$, while metabolic acidosis and alkalosis are respectively compensated by hypocapnia and hypercapnia. However, describing primary acid-base disturbances and compensatory responses in terms of $[\text{HCO}_3^-]$ provides little physiological information since physicochemical principles dictate that $[\text{HCO}_3^-]$ is a reflection of the prevailing $[\text{SID}]$ and $[\text{A}_{\text{TOT}}]$, and, the former can be altered by changes in $[\text{Na}^+]$, $[\text{Cl}^-]$ or both. Using physicochemical principles, a primary pathological or physiological disturbance in $[\text{SID}]$, PCO_2 or $[\text{A}_{\text{TOT}}]$, can be seen to force the system from one state to another by initiating a compensatory response in one or more of the remaining two independent variables. If the compensatory response is both of sufficient magnitude and is metabolically sustainable, the acid-base status enters a different steady state. The normal values for $[\text{SID}]$, PCO_2 and $[\text{A}_{\text{TOT}}]$ should then be re-defined in this new steady state. The remainder of this chapter will focus on an examination of how normal $[\text{SID}]$ changes in response to chronic hypercapnia, hypocapnia and hypoproteinemia.

10.7 HYPERCAPNIA

Traditionally, a sustained elevation in PCO_2 is said to be compensated by an increase in $[\text{HCO}_3^-]$ and hypochloremia. Earlier studies [13, 18-20] explained this as a renal/cellular mediated increase in $[\text{HCO}_3^-]$ being responsible for the decrease in $[\text{Cl}^-]$. However, physicochemical principles dictate that chronic hypercapnia stimulates a reduction in $[\text{Cl}^-]$, thus lowering $[\text{SID}]$ and increasing $[\text{HCO}_3^-]$ through physical chemistry. Conceptually then, the new, increased $[\text{SID}]$ is the expected normal value during sustained hypercapnia. Re-establishment of $[\text{SID}]$ to a different norm can theoretically occur from either change in $[\text{Cl}^-]$, change in $[\text{Na}^+]$, or both. However, as discussed by Stewart (chapter 9) and Kellum, [3] regulation of plasma $[\text{Cl}^-]$ is probably the major mechanism by which plasma $[\text{SID}]$ can be manipulated. Plasma $[\text{Na}^+]$ is rigidly regulated by the interaction of the numerous endocrinological influences serving to maintain water and volume homeostasis. Conversely, $[\text{Cl}^-]$ is readily increased or decreased, independently of plasma sodium, by shifting across cellular membranes from simple Donnan forces or alteration in renal excretion. Alfero et al. [21] demonstrated similar findings in patients with chronic obstructive pulmonary disease (COPD) and retained CO_2 . The increase in $[\text{HCO}_3^-]$ observed with chronic hypercapnia was accounted for by an increase in $[\text{SID}]$ mainly due to a