Different Interpretation Approaches To Acid Base Disturbances

An Essay
Submitted For Partial Fulfillment Of Master Degree In Anesthesia
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2011

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"If anyone killed a person not in retaliation of murder, or (and) to spread mischief in the land - it would be as if he killed all mankind, and if anyone saved a life, it would be as if he saved the life of all mankind"

Al-Maidah-32

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Dedicated
To My Father
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:::::: Acknowledgement ::::::

Before all, I should express my deep thanks to **ALLAH**, *without His great blessings I would have never accomplished my work.*

It is a great pleasure and honor to work under the supervision of **Prof. Dr.Gamal Eldin Mohammad Ahmad Elewa**, *Professor Of Anesthesia And Intensive Care, his modesty, honesty, and patiently have affected me much. I am greatly honored to express my deepest gratitude to him.*

I wish to express my deep thanks to **Prof. Dr.Azza Atef Abd Al-Alim Shabaan**, *Assistant Professor Of Anesthesia And Intensive Care. Her kind guidance, continuous supervision, and president encouragement helped me a lot to finish this work.*

It is my great pleasure to express my appropriation of all the efforts provided by **Dr. Hanaa Mohamed Abd Allah El Gendy**, *Lecturer Of Anesthesia And Intensive Care. Her continues support, meticulous revision are much beyond praise.*

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List Of Abbreviations

ICF	Intracellular Fluid
ECF	Extracellular Fluid
RBCs	Red Blood Cells
AG	Anion Gap
UA	Unknown Anions
UC	Unknown Cations
UMA	Unmeasured anions
SID	Strong Ion difference
A_{TOT}	Total Acids
HA	Weak Electrolyte
SIDa	Apparent Strong Ion difference
SIDe	Effective Strong Ion difference
SIG	Strong Ion Gap
XA	Unknown Anions
BE	Base Excess
SBE	Standard Base Excess
SBEc	Corrected Standard Base Excess
BD	Base Deficit
$Citrate_{TOT}$	Total citrate
Alb	Albumin
Pi_{TOT}	Total Phosphate
PaCO2	Partial CO2 Tension
C_{Alb}	albumin concentration
C_{Phos}	phosphate concentration

::::::Introduction::::::

The chemical composition of the extracellular and intracellular spaces is tightly controlled; this includes, but is not limited to, hydrogen and hydroxyl moieties. Alterations in the relative concentrations of these ions, widely described as disorders of acid-base chemistry, are associated with significant clinical problems. Consequently, the detection, interpretation, and treatment of acid-base abnormalities have become a core element of clinical care. Many clinicians struggle to understand acid-base chemistry because traditional educational approaches have focused on interpretation of laboratory data, rather than an understanding of underlying biophysical chemistry. The modern physical-chemical approach to acid-base balance has significantly enhanced understanding of these problems and simplified the clinical approach [1].

Almost a century ago, Henderson used an equilibrium theory of carbonate species to suggest a physiochemical approach to acid-base balance in human blood. Later, Hasselbalch provided a simple formula (the Henderson-Hasselbalch Equation) to describe those equilibria. Thereafter, Van Slyke realized the importance of noncarbonate buffers, principally hemoglobin and proteins, in the regulation of acid-base behavior. Siggaard-Anderson and others have developed the standard (base excess) model of acid-base balance in common use .Corey in 2003 claimed that this model is relatively easy to understand, simple mathematically, and relies on easy-to-measure variables[2].

At the heart of the physical-chemical approach to understanding acidbase is the fact that traditional approaches adapted from Henderson and Hasselbalch or those proposed by Siggaard-Andersen et al. are inadequate to understand mechanism of acid base disturbance[3].

Stewart, a Canadian physiologist, proposed a radically different approach to acid-base balance. He started by discarding many of the features of the traditional model, including the standard notions of acids and bases.

Based upon the laws of mass action, the conservation of mass and the conservation of charge, he derived relatively complex mathematical formulas to describe acid-base balance, while introducing two new variables, the strong ion difference (SID) and the total weak acids (A_{TOT}).

Recent advances in whole body acidbase physiology as well as epidemiology have resulted in a much clearer picture of metabolic acidbase disturbances in the critically ill. It is now possible to 'unify' traditional descriptive approaches to acid-base balance with modern quantitative techniques. This unified approach is both simple and transparent and can be easily used at the bedside [4].

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:::::Aim Of Work::::::

- Understanding basic concept of pH ,and Hydrogen ion activity.
- Understanding different definitions of acidosis, alkalosis.
- Development of traditional approach using combination of Henderson-Haselblach equation, the base excess and its clinical application.
- Development of Stewart approach, its mathematical concept and its clinical application.
- Unification of acid-base physiology.

Chapter 1

Basic Principles And Terminologies

A Terminologies

I Various theories of Acid And Base

The word "acid" is derived from Latin word ascidus which means sour, first description was done by Arrhenius in 1887, he defined acid as a substance which was capable of dissociating in water producing hydrogen ion and defined base as a substance which was capable of dissociating in water producing hydroxide. Later in 1932 Bronsted-Lowery theory introduced acid as hydrogen ion donor and substance that accept hydrogen ion as conjugate base. It determined strength of acid by its tendency to donate hydrogen ion to solvent. In 1923, Lews produced more general definition; he defined acid as potential electron pair acceptor and base as potential electron pair donor. Later in 1939, Usanovich theory has consolidated the previous approaches to define acid as substance that donate cation, or accept an anion or electron, and base as substance that donate an anion or accept cation. In this essay, we will use combination of Arrhenius approach as (acid: Hydrogen ion in solution) and Bronsted-Lowery theory as (acid: Proton donor)[5, 6, 7].

II Hydrogen ion concentration and activity

Activity is a measure of the "effective concentration" of a species in a mixture. Activity indicates how many particles seem to be present in the solution and it's different from how many actually are present. Activity is related to concentration by the activity coefficient.The activity of an ion is determined by

the following equation

$$a_x = q.[x]$$

a_x = activity of substance x in the solution .
q = activity coefficient of x .
$[x]$ = concentration of substance x in the solution .

The activity coefficient of a solute is constant in any particular given solution but its value can change if the properties of the solution are changed (e.g by changing the ionic strength or the temperature). If the relationship between concentration and activity is plotted on a graph, it is not linear. It depends on the type of solvent, the type, and concentration of the various solutes present in the solution. In an ideal solution, the activity coefficient is one. The activity coefficient also approaches unity as non-ideal solutions become more and more diluted[11].

III pH

Is the negative logarithm of hydrogen ion concentration expressed by following equation :

$$pH = -Log_{10}H^+$$

Conversion between pH, H

Hydrogen ion concentration of 158 nanomole/l will give the following pH

$$pH = -Log_{10}(158 \times (10^{-9}))$$

$$pH = 1/Log_{10}(158 \times (10^{-9})) = 6.8$$

So if accepted pH varies between 7.3-7.5, its hydrogen ion concentration will be 50 nanomole/l and 31 nanomole/l respectively[5].

IV K_a *and* pK_a

An acid dissociation constant, K_a, (also known as acidity constant, or acid-ionization constant) is a quantitative measure of the strength of an acid in solution. It is the equilibrium constant for a chemical reaction known as dissociation in the context of acid-base reactions. The equilibrium can be written symbolically as:

$$HA \Longleftrightarrow A^- + H^+$$

Where HA is a generic acid that dissociates by splitting into A, known as the conjugate base of the acid, and the hydrogen ion or proton, H^+, which, in the aqueous solutions, exists as a solvated hydronium ion, the chemical species HA, A and H^+ are said to be in equilibrium when their concentrations do not change with the passing of time. The dissociation constant is usually written as a quotient of the equilibrium

$$K_a = \frac{[A^-][H^+]}{AH}$$

Due to the many orders of magnitude spanned by K_a values, a logarithmic measure of the acid dissociation constant is more commonly used in practice. pKa, which is equal to Log_{10} K_a, may also be referred to as an acid dissociation constant

$$pK_a = -Log_{10}K_a$$

The larger the value of pK_a, the smaller the extent of dissociation. A weak acid has a pK_a value in the approximate range -2 to 12 in water. Acids with a pK_a value of less than -2 are said to be strong acids; a strong acid is almost completely dissociated in aqueous solution, to the extent that the concentration of the undissociated acid becomes undetectable[7, 11].

V Law of mass action

In chemistry, the law of mass action is a mathematical model that explains and predicts behaviors of solutions in dynamic equilibrium. It can be described with two aspects: The equilibrium aspect, concerning the composition of a reaction mixture at equilibrium, and the kinetic aspect, concerning the rate equations for elementary reactions. Both aspects stem from the research by

Guldberg and Waage (1864-1879) in which equilibrium constants were derived by using kinetic data and the rate equation which they had proposed. Guldberg and Waage also recognized that chemical equilibrium is a dynamic process in which rates of reaction for the forward and backward reactions must be equal.

The law of mass action is universal, applicable under any circumstance. However, for reactions that are complete, the result may not be very useful. By using a general chemical reaction equation in which reactants A and B react to give product C and D

$$aA + bB \rightarrow cC + dD$$

where a, b, c, d are the coefficients for a balanced chemical equation.
The mass action law states that if the system is at equilibrium at a given temperature, then the following ratio is a constant.

$$K_{eq} = \frac{([C]c[D]d)}{([A]a[B]b)}$$

The square brackets "[ ]" around the chemical species represent their concentrations[9].

VI Buffering

It's substance that counteracts effects of pH of acid or base or, it's a solution containing substance which has ability to minimize change in pH when acid or base is added to it. *(Table 1)* contains different buffers in the body and its site of action[10].

1. **Bicarbonate /Carbon Dioxide buffer system**
   On exposure to water four things can happen to carbon dioxide

   (a) CO_2 can dissolve :

   $$CO_2\text{[gas form]} \Longleftrightarrow CO_2\text{[Dissolved form]}$$

   This reaction can be go in forward direction (from gas form to dissolved form) depending on partial pressure of CO2 or reverse direction (from dissolved form to gas form) depending on concentration of dissolved CO2

   $$CO_2"Dissolved" = 0.03 \times (PaCO_2)$$

Table 1: Major Body Buffering System[10]

Site	Buffer System	Comment
Interstitial fluid	Bicarbonate	For metabolic acids
	Phosphate	Not important concentration too low
	Protein	Not important because concentration too low
Blood	Bicarbonate	Important for metabolic acids
	Hemoglobin	Important for carbon dioxide
	Plasma protein	Minor buffer
	Phosphate	Concentration too low
Intracellular Fluid	Proteins	Important buffer
	Phosphates	Important buffer
Urine	Phosphate	Responsible for most of 'Titratable Acidity'
	Ammonia	Important - formation of NH_4^+
Bone	Ca carbonate	

$$CO_2\text{"}Dissolved\text{"} = 0.03 \times (40) = 1.2\ mmol/L$$

where 0.03 is solubility constant for CO2 in plasma

(b) CO_2 can react with water (formation of carbonic acid)

$$CO_2 + H_2O \Longleftrightarrow H_2CO_3^{-2}$$

The reaction of CO2 with water is slow with half life of about 30 seconds ,This reaction is seeded up by carbonic anhydrase enzyme present in certain tissues such as red blood cells and renal tubular epithelium.

(c) Carbonic acid can be dissociated into hydrogen ion and bicarbonate ion

$$H_2CO_3 \Longleftrightarrow H^+ + HCO_3^-$$

(d) Bicarbonate $HCO3^-$ can dissociate into hydrogen and carbonate ions

$$HCO3^- \Longleftrightarrow H^+ + CO3^{-2}$$

Since pK_a of this reaction is 9.8, So the only trace amount of carbonate are present in physiological pH range[11]

Law of mass action for bicarbonate /Carbon dioxide buffer system:

Since the concentration of H_2CO_3 is low in relation to CO2 Dissolved and

HCO_3^- the reactions can be simplified to

$$CO_2[dissolved] + H_2O \Longleftrightarrow H^+ + HCO_3^-$$

By application of law of mass action:

$$K_a = \frac{[H][HCO_3]}{CO_2[Dissolved][H_2O]}$$

Since the concentration of water is constantK_a and H_2O can be replaced by$K_a^{'}$

$$K_a^{'} = K_a \times H_2O$$

$$K_a^{'} = \frac{[H][HCO3^-]}{CO_2[Dissolved]}$$

$$H^+ = \frac{K_a^{'} \times CO_2[Dissolved]}{HCO3}$$

Substituting K'a by 800 nmol/L (value of plasma at 37C)

$$H^+ = \frac{800 \times 0.03 \times PaCO2}{[HCO_3^-]}$$

Taking log10 of both sides

$$pH = 6.1 + \frac{Log_{10}[HCO_3^-]}{0.03 \times PCO_2}$$

$$pH = 6.1 + Log_{10}\frac{HCO_3^-}{0.03 \times (PCO_2)}$$

Henderson Hasselbalch equation

On chemical ground, substance at pK_a 6.1 should not be good buffer at pH 7.40, but since PCO_2 can be regulated by alveolar ventilation, this system is able to buffer very effectively[1, 9, 11].

2. **The phosphate buffer system**
   The concentration of phosphate in the blood is so low that it is quantitatively unimportant. Phosphates are important buffers intracellularly and in urine where their concentration is higher.
   Phosphoric acid is a triprotic weak acid and has a pKa value for each of the three dissociations:

$$H_3PO_4 \Longleftrightarrow H^+ + H_2PO4^-$$

$$pK_a1 = 2$$

$$H^+ + H_2PO_4^- \Longleftrightarrow H^+ + HPO_4^{-2}$$

$$pK_a2 = 6.8$$

$$H^+ + HPO_4^{-2} \Longleftrightarrow PO_4^{-3} + H^+$$

$$pK_a3 = 12$$

   At the prevailing pH values in most biological systems, monohydrogen phosphate and dihydrogen phosphate are the two species present. The pK_a2 is 6.8 and this makes the closed phosphate buffer system a good buffer intracellularly and in urine. The pH of glomerular ultrafiltrate is 7.4 and this means that phosphate will initially be predominantly in the monohydrogen form and so can combine with more H^+ in the renal tubules. *This makes the phosphate buffer more effective in buffering against a drop in pH than a rise in pH [12].*

3. **Protein buffer system**
   Protein buffer system depends on free and terminal amino acids that respond to pH changes by accepting or releasing H^+. If pH rises, Carboxyl group of amino acid dissociates, acting as weak acid, releasing a hydrogen ion. If pH drops, carboxylate ion and amino group act as weak bases by accepting H^+ , forming carboxyl group and amino ion.
   Proteins that contribute to buffering capabilities: plasma proteins, proteins in interstitial fluid, and proteins in intracellular fluid (ICF). As buffering occurs by imidazole group of the histidine residues, hemoglobin is quan-

titatively about 6 times more important than the plasma proteins as it presents in about twice the concentration of plasma proteins and contains about three times the number of histidine residues per molecule[13].

B Different acid base disturbances

I Metabolic Acidosis

Definition

Abnormal primary process or condition leading to an increase in fixed acids in the blood[14].

Anion Gap Approach

The most widely used tool for investigating metabolic acidosis is the anion gap. The term anion gap (AG) represents the concentration of all the unmeasured anions in the plasma.
The negatively charged proteins account for about 10% of plasma anions and make up the majority of the unmeasured anion represented by the anion gap under normal circumstances. The acid anions (eg. lactate, acetoacetate, sulphate) produced during a metabolic acidosis are not measured as part of the usual laboratory biochemical profile. The H^+ produced reacts with bicarbonate anions (buffering) and the CO2 produced is excreted via the lungs.
The net effect is a decrease in the concentration of measured anions (ie. $HCO3^-$) and an increase in the concentration of unmeasured anions (the acid anions) so the anion gap increases*(Table 2)*[15]. The sum of the difference in charge of the common extracellular ions reveals an unaccounted for "gap" of 10 to 12 mEq/L [16]*(Figure 1)*

$$\text{Anion gap} = (Na^+ + K^+ - (Cl^- + HCO_3^-))$$

Usually only cations sodium and potassium and the anions chloride and bicarbonate are measured, therefore remaining cations and anions are designated as unmeasured cations (UC) and unmeasured anions (UA)

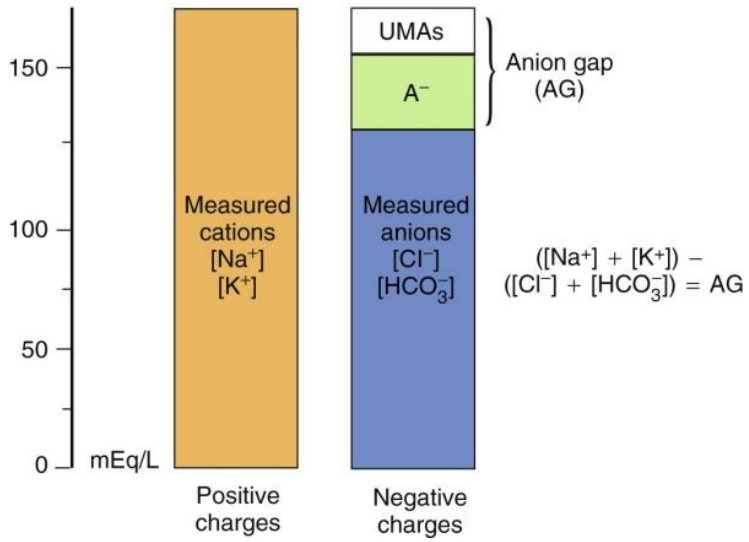

Figure 1: The anion gap represents the difference in charge between measured cations and measured anions [1].

$$Na^+ - (Cl^- + HCO3^-) = UA - UC = AnionGap$$

Table 2: Unmeasured anions and cations[16]

Albumin : 15 mEq/l	Ca: 5 mEq/l
Organic Acid : 5 mEq/l	K :4.5 mEq/l
Phosphate: 2 mEq/l	Mg: 1.5 mEq/l
Sulfate : 1 mEq/l	

Albumin is major source of unmeasured anion so reduction of its level will cause reduction of anion gap. A 50% reduction in concentration of albumin level will cause 75% reduction in the anion gap value.

$$Adjusted\ anion\ gap = \\ Observed\ anion\ gap + 2.5(4.5 - measured\ \ albumin\ \ g/dL)$$

According to normal or elevation of value of anion gap, metabolic acidosis

can be classified as High anion gap metabolic acidosis and normal anion gap metabolic acidosis[16].

1. **High anion gap metabolic acidosis**
   When fixed acid is added to extracellular space , the acid dissociates producing hydrogen ions and anions, The hydrogen ions combine to with bicarbonate to form carbonic acid, this will decrease the value of $HCO3^-$ resulting in increasing value of anion gap *(Table 2)*[15, 17, 18].

   Causes

   (a) Ketoacidosis
   - Diabetic ketoacidosis
   - Alcoholic ketoacidosis
   - Starvation ketoacidosis

   (b) Lactic Acidosis
   - Type A Lactic acidosis (Impaired perfusion)
   - Type B Lactic acidosis (Impaired carbohydrate metabolism)

   (c) Renal Failure

   (d) Toxins
   - Ethylene glycol
   - Methanol
   - Salicylates

2. **Normal anion gap metabolic acidosis**
   If metabolic acidosis was caused by loss of bicarbonate from extra cellular fluid, this loss is counter balanced by gain of chloride ions or maintenance of electrical neutrality, so the relationship ($AG = Na^+ - (Cl^- + HCO3)^-$)remains unchanged due to balance between the chloride and $HCO3^-$.

Causes[14]

1. Renal Causes :

- Renal tubular acidosis
- Carbonic anhydrase inhibitors
- Hypoaldosteronism

2. GIT Causes:
   - Severe diarrhea
   - Uretero-enterostomy or obstructed ileal conduit.
   - Drainage of pancreatic or biliary secretions.
   - Small bowel fistula.
3. Other Causes:
   - Addition of HCl, NH4Cl
   - Hypoparathyrodism
   - Infusion of isotonic saline
   - Total parenteral Nutrition (TPN)

Other Tools That used in evaluation of metabolic Acidosis

1. **Delta ratio**

$$\text{Delta ratio } = \Delta\text{Anion gap}/\Delta[HCO_3^-]$$

$$= \frac{\text{Measured anion gap} - \text{Normal anion gap}}{\text{Normal}[HCO3^-] - \text{Measured}[HCO3^-]}$$

$$\frac{(AG - 12)}{(24 - [HCO_3^-])}$$

If one molecule of metabolic acid (HA) is added to the ECF and dissociates, the one H^+ released will react with one molecule of HCO_3^- to produce CO_2 and H_2O. This is the process of buffering. The net effect will be an increase in unmeasured anions by the one acid anion A- (ie anion gap increases by one) and a decrease in the bicarbonate by one mEq.

Now, if all the acid is dissociated in the ECF and all the bufferring is by bicarbonate, then the increase in the AG should be equal to the decrease in bicarbonate so the ratio between these two changes (which we call the delta ratio) should be one.

As described previously, more than 50% of excess acid is buffered intracellularly and by bone, not by $HCO3^-$. In contrast, most of the excess anions remain in the ECF, because anions cannot easily cross the lipid bilayer of the cell membrane. As a result, the elevation in the anion gap usually exceeds the fall in the plasma [$HCO3^-$]. In lactic acidosis, for example, the delta ratio averages 1.6:1.

On the other hand, although the same principle applies to ketoacidosis, the ratio is usually close to 1:1 in this disorder because the loss of ketoacids anions (ketones) lowers the anion gap and tends to balance the effect of intracellular buffering. Anion loss in the urine is much less prominent in lactic acidosis because the associated state of marked tissue hypoperfusion usually results in little or no urine output.

A delta-ratio value below 1:1 indicates a greater fall in $[HCO3^-]$ than one would expect given the increase in the anion gap. This can be explained by a mixed metabolic acidosis, i.e a combined elevated anion gap acidosis and a normal anion gap acidosis, as might occur when lactic acidosis is superimposed on severe diarrhea. In this situation, the additional fall in $HCO3^-$ is due to further buffering of an acid that does not contribute to the anion gap. (i.e addition of HCl to the body as a result of diarrhea)

A value above 2:1 indicates a lesser fall in $[HCO3^-]$ than one would expect given the change in the anion gap. This can be explained by another process that increases the $[HCO3^-]$,i.e. a concurrent metabolic alkalosis. Another situation to consider is a pre-existing high $HCO3^-$ level as would be seen in chronic respiratory acidosis[18, 19].

2. **Urinary anion gap**

Measurement of the urine anion gap (AG) and urine osmolal gap may be helpful in the evaluation of patients with a normal AG (hyperchloremic) metabolic acidosis by providing an estimate of urinary ammonium excretion
The urine AG is calculated from the difference between the measured cations (Na^+ and K^+) and the measured anion (Cl^-):

$$\text{Urine AG} = \text{Urine}(Na^+ + K^+ - Cl^-)$$

The urine AG has a negative value in most patients with a normal AG metabolic acidosis due to the appropriate increase in urinary ammonium in an attempt to excrete the excess acid. Ammonium is an unmeasured cation; as a result, an increase in its excretion as NH4Cl will lead to a rise in the urine Cl concentration and a negative urine AG, usually ranging from -20 to -50 meq/L.

In contrast, if there is an impairment in kidney function resulting in an inability to increase ammonium excretion (i.e. Renal Tubular Acidosis), then Cl- ions will not be increased in the urine and the urine anion gap will not be affected and will be positive or zero.

In a patient with a hyperchloremic metabolic acidosis: A negative UAG suggests GI loss of bicarbonate (eg diarrhea), a positive UAG suggests impaired renal acidification (ie. renal tubular acidosis)[20, 21, 22].

3. **Osmolar gap**

The plasma osmolality is determined by the concentrations of the different solutes in the plasma. In normal subjects, sodium salts (chloride and bicarbonate), glucose, and urea are the primary circulating solutes. Although a variety of formulas have been evaluated to predict the plasma osmolality ,

most studies have concluded that plasma osmolality can be best estimated from the following formula :

$$\text{Calculated Plasma Osmolarity} = (2([Na^{+}]))+\frac{\text{[glucose, in mg/dL]}}{18}+\frac{BUN}{2.8}$$

Na is Plasma Sodium level
BUN is Blood Urea Nitrogen

The Osmolar Gap is another important diagnostic tool that can be used in differentiating the causes of elevated anion gap metabolic acidosis.. Plasma osmolality (Posm) can also be measured directly by freezing point depression. The osmolar gap is the difference between the calculated serum osmolarity and the measured serum osmolarity.

The plasma sodium is multiplied by two to account for accompanying anions (chloride and bicarbonate) and, the divisors 18 and 2.8 convert units of mg/dL into mosmol/kg

The normal osmolar gap is 10-15 mmol/L H_20 .The osmolar gap is increased in the presence of low molecular weight substances that are not included in the formula for calculating plasma osmolarity. Common substances that increase the osmolar gap are ethanol, ethylene glycol, methanol, acetone, isopropyl ethanol and propylene glycol[23, 24, 25].

Clinical effect of metabolic acidosis[14]

A metabolic acidosis can cause significant physiological effects, particularly affecting the respiratory and cardiovascular systems.

1. **Respiratory Effects**
    - Hyperventilation (Kussmaul respirations)
    - Shift of oxyhaemoglobin dissociation curve (ODC) to the right

- Decreased 2,3 DPG levels in red cells (shifting the ODC back to the left)

2. **Cardiovascular Effects**

- Depression of myocardial contractility
- Sympathetic overactivity (tachycardia, vasoconstriction,decreased arrhythmia threshold)
- Resistance to the effects of catecholamines
- Peripheral arteriolar vasodilatation
- Venoconstriction of peripheral veins
- Vasoconstriction of pulmonary arteries
- Effects of hyperkalaemia on heart

3. **Other Effects**

- Increased bone resorption (chronic acidosis only)
- Shift of K^+ out of cells causing hyperkalaemia

Respiratory Compensation of metabolic acidosis

Once a metabolic acidosis is suspected by low bicarbonate concentration, an arterial blood gas analysis should be obtained. The low HCO3 level can be caused either by a primary metabolic acidosis or as the metabolic compensation for a respiratory alkalosis. The direction of the pH will separate metabolic acidosis (pH $<$ 7.35) from a respiratory alkalosis (pH $>$ 7.45)[26].

The normal respiratory response to a metabolic acidosis is a decrease in PaCO2. This is given by the Winter's equation:

$$PaCO2 = 1.5 \times (\text{observed } HCO3^-) + 8 \pm 2$$

(A quick rule of thumb: the PaCO2 should approximate the last two digits of pH. For example, pH 7.25, PaCO2 should be close to 25 mm Hg.)

Failure to have an appropriate respiratory response to metabolic acidosis represents a failure of airway and/or breathing, which must be addressed before any other workup commences[14].

Management of metabolic acidosis

The treatment of metabolic acidosis usually directed to treatment of underlying cause [18]:
For example :

- Insulin, fluid, potassium administration and phosphorus replacement if needed in case of diabetic ketoacidosis.
- Restoration of intravascular volume for improving perfusion in hypovolemic patient
- Dialysis for renal failure.

Role of alkali therapy for metabolic acidosis:

1. **In normal anion gap type**
   Bicarbonate administration is indicated since there is no endogenous acid anions which can be metabolized by the liver.
2. **In high anion gap metabolic acidosis**
   Bicarbonate infusion is not recommended in high anion gap metabolic acidosis type unless facing a setting of severe metabolic acidosis (pH$<$7.1) where the patient is deteriorating rapidly.
   A trial infusion of bicarbonate can be attempted by administering one-half of the estimated bicarbonate deficit

   $$\text{HCO3}^{-} \text{ deficit (mEq)} = 0.6 \times \text{wt(kg)} \times \text{ (15-measured bicarbonate)}$$

   Infusion continuity is guided by cardiovascular status improvement, infusion should continue till targeted HCO_3^- equals 15 mEq/L, if there is no improvement or further deterioration, further bicarbonate is not

warranted[16, 27, 28].

Alternatives of bicarbonate:

- **Cabicarb**
  Cabicarb is considered as buffer solution that has mixture of sodium bicarbonate and disoduim carbonate with ratio 1:1, so it has less bicarbonate and much less CO2 than standered 8.4 % sodium bicarbonate solution [29].
- **THAM**
  Tris-hydroxymethyle anminomethane (THAM), is a weak base that is used as superior alternative to bicarbonate for treatment of metabolic acidosis as it has greater buffering capacity(its pKa is 7.82), and protonated THAM is execrated in urine so CO2 production is not increased[30].

Surviving Sepsis Campaign in its guidelines published in 2008 recommended avoidance of use of bicarbonate therapy for managing septic shock for purpose of improving heamodynamics or reducing vasopressor requirement in treating lactic acidosis associated with hypoperfusion when pH more than 7.15 [31]

European Resuscitation Council (ERC) guidelines published in 2010 recommended avoidance of routine bicarbonate therapy during cardiac arrest and CPR and it is recommended only in case of hyperkalemia or tricyclic antidepressant toxicity[32].

II Metabolic Alkalosis

Definition

Abnormal primary process that cause plasma bicarbonate to rise to a level higher than expected[33]

Predisposing conditions

Metabolic alkalosis may be generated by one of the following mechanisms:

1. **Loss of hydrogen ions:**
   Whenever a hydrogen ion is excreted, a bicarbonate ion is gained into the extracellular space. Hydrogen ions may be lost through the kidneys or the GI tract. Vomiting or nasogastric (NG) suction generates metabolic alkalosis by the loss of gastric secretions, which are rich in hydrochloric acid (HCl). Renal losses of hydrogen ions occur whenever the distal delivery of sodium increases in the presence of excess aldosterone, which stimulates the electrogenic epithelial sodium channel (ENaC) in the collecting duct. As this channel reabsorbs sodium ions, the tubular lumen becomes more negative, leading to the secretion of hydrogen ions and potassium ions into the lumen.

2. **Shift of hydrogen ions into the intracellular space:**
   This mainly develops with hypokalemia. As the extracellular potassium concentration decreases, potassium ions move out of the cells. To maintain neutrality, hydrogen ions move into the intracellular space.

3. **Alkali administration:**
   Administration of sodium bicarbonate in amounts that exceed the capacity of the kidneys to excrete this excess bicarbonate may cause metabolic alkalosis. This capacity is reduced when a reduction in filtered bicarbonate occurs, as observed in renal failure, or when enhanced tubular reabsorption of bicarbonate occurs, as observed in volume depletion .

4. **Contraction alkalosis:**
   Loss of bicarbonate-poor, chloride-rich extracellular fluid, as observed with thiazide diuretic or loop diuretic therapy or chloride diarrhea, leads to contraction of extracellular fluid volume. Because the original bicarbonate mass is now dissolved in a smaller volume of fluid, an increase in bicarbonate concentration occurs. This increase in bicarbonate causes, at most, a -2 to -4 mEq/L rise in bicarbonate concentration.

Causes

The most common causes of metabolic alkalosis are the use of diuretics and the external loss of gastric secretions. Causes of metabolic alkalosis can be divided into chloride-responsive alkalosis (urine chloride <20 mEq/L), chloride-resistant alkalosis (urine chloride >20 mEq/L).

1. **Chloride-responsive Alkalosis (Urine Chloride <20 mEq/L)**

   (a) **Loss of gastric secretions**
   Gastric secretions are rich in HCl. The secretion of HCl by the stomach usually stimulates bicarbonate secretion by the pancreas once HCl reaches the duodenum. Ordinarily, these substances are neutralized, and no net gain or loss of hydrogen ions or bicarbonate occurs. When HCl is lost by vomiting or NG suction, pancreatic secretions are not stimulated and a net gain of bicarbonate into the systemic circulation occurs, generating a metabolic alkalosis. Volume depletion maintains alkalosis. In this case, the hypokalemia is secondary to the alkalosis itself and to renal loss of potassium ions from the stimulation of aldosterone secretion.

   (b) **Ingestion of large doses of nonabsorbable antacids**
   Ingestion of large doses of nonabsorbable antacids (eg, magnesium hydroxide) may generate metabolic alkalosis by a rather complicated mechanism. Upon ingestion of magnesium hydroxide, calcium, or aluminum with base hydroxide or carbonate, the hydroxide anion buffers hydrogen ions in the stomach. The cation binds to bicarbonate secreted by the pancreas, leading to loss of bicarbonate with stools. In this process, both hydrogen ions and bicarbonate are lost, and, usually, no acid-base disturbance occurs. Sometimes, not all the bicarbonate binds to the ingested cation, which means that some bicarbonate is reabsorbed in excess of the lost hydrogen ions. This occurs primarily when antacids are administered with a cation-exchange resin (eg, sodium polystyrene sulfonate [Kayexalate]); the resin binds the cation, leaving bicarbonate unbound.

   (c) **Thiazide or loop diuretics**
   Thiazides and loop diuretics enhance sodium chloride excretion in the

distal convoluted tubule and the thick ascending loop, respectively. These agents cause metabolic alkalosis by chloride depletion and by increased delivery of sodium ions to the collecting duct, which enhances potassium ion and hydrogen ion secretion. Volume depletion also stimulates aldosterone secretion, which enhances sodium ion reabsorption in the collecting duct and increases hydrogen ion and potassium secretion in this segment. Urine chloride is low after discontinuation of diuretic therapy, while it is high during active diuretic use

2. **Chloride-resistant Alkalosis (urine chloride >20 mEq/L)**

   (a) **Chloride-resistant alkalosis with hypertension**
   An adrenal adenoma (most common), bilateral adrenal hyperplasia, or an adrenal carcinoma may cause primary hyperaldosteronism. Another cause of primary hyperaldosteronism is glucocorticoid-remediable aldosteronism, an autosomal dominant disorder, in which ectopic production of aldosterone in the zona fasciculata of the adrenal cortex occurs. This type of primary hyperaldosteronism is responsive to glucocorticoid therapy, which inhibits aldosterone secretion by suppressing ACTH.

   (b) **Chloride-resistant alkalosis (urine chloride >20 mEq/L) with hypotension or normotension**
   Bartter syndrome is an inherited autosomal recessive disorder, in which reabsorption of sodium ions and chloride ions in the thick ascending loop of Henle is impaired, leading to their increased delivery to the distal nephron. This condition and the subsequent salt depletion and stimulation of the renin-angiotensin-aldosterone system lead to enhanced secretion of hydrogen and potassium ions
   Pure hypokalemia (ie, severe potassium ion depletion) causes mild metabolic alkalosis, but, in combination with hyperaldosteronism, the alkalosis is more severe. Possible mechanisms of alkalosis in hypokalemia are enhanced proximal bicarbonate reabsorption, stimulated renal ammonia genesis, impaired renal chloride reabsorption, reduced GFR (in animals), and intracellular acidosis in the distal nephron with subsequent enhanced hydrogen

secretion.
Magnesium depletion (ie, hypomagnesemia) may lead to metabolic alkalosis. The mechanism probably is caused by hypokalemia, which is usually caused by or associated with magnesium depletion[33, 34, 35].

Clinical effect of metabolic alkalosis

The effects of the alkalosis are often difficult to distinguish from the effects of associated problems such as hypovolaemia, potassium and chloride depletion.This makes it more difficult to characterize the effects of the alkalosis itself[34].

1. Decreased myocardial contractility
2. Dysrhythmias
3. Decreased cerebral blood flow
4. Confusion
5. Mental obtundation
6. Neuromuscular excitability
7. Impaired peripheral oxygen unloading (due shift of oxygen dissociation curve to left).

Compensation

"The compensatory response is hypoventilation"

The hypoventilation causes a compensatory rise in arterial PaCO2 but the magnitude of the response has generally been found to be quite variable. More recent studies have almost invariably shown that hypoventilation does reliably occur in metabolic alkalosis.
This has been attributed to various problems with some of the older studies which did not account for the presence of conflicting factors, particularly those causing hyperventilation:

1. **Hyperventilation due to pain.**
   in response to the stress of a painful arterial puncture. This could lower the measured PaCO2 during the procedure.

2. **Hyperventilation due to pulmonary congestion.**
   Some patients with metabolic alkalosis due to diuretic use have subclinical pulmonary congestion sufficient to stimulate intrapulmonary receptors and cause tachypnoea and give a sensation of dyspnoea. This slight hyperventilation is sufficient to negate the rise in arterial PaCO2.

3. **Hyperventilation due to hypoxaemia.**
   An associated hypoxaemia will stimulate the peripheral chemoreceptors and cause hyperventilation if the arterial pO2 is below 50 to 55mmHg. This may not have been considered in early studies[33, 34].

This common association of metabolic alkalosis with factors causing hyperventilation probably accounts for most of the past findings of variability of the change in arterial PaCO2.

The expected PaCO2 due to appropriate hypoventilation in simple metabolic alkalosis can be estimated from the following formula:

$$\text{Expected PaCO2} = 0.7 \times [HCO3^{-}] + 20mmHg(\text{range: } \pm 5)$$

Management:

1. **Chloride-Responsive Alkalosis**
   Although replacement of the chloride deficit is essential, selection of the accompanying cation sodium, potassium or proton is dependent on assessment of ECF volume status, the presence and degree of associated potassium depletion, and the degree and reversibility of any depression of GFR. If kidney function is normal, bicarbonate and base equivalents will be excreted with sodium or potassium and metabolic alkalosis will be rapidly corrected as chloride is made available.
   If depletion of chloride and ECF volume coexist, as is most common, **isotonic NaCl** is the appropriate therapy and simultaneously corrects both deficits. In patients with overt signs of volume contraction, the administration of a minimum of 3 to 5 L of 150 mEq/L NaCl is usually necessary

to correct volume deficits and metabolic alkalosis. When the ECF volume is assessed as normal, total body chloride deficit can be estimated by the formula:

0.2 x Body weight (kg) x Desired increment in plasma chloride (mEq/L)

The replacement of continuing losses of fluid and electrolytes must be added to this regimen. As the chloride deficit is corrected, a brisk alkaline diuresis will occur with a decrease in plasma bicarbonate toward normal. Plasma potassium concentration should be followed serially. Concomitant potassium repletion is clinically indicated to avoid other potentially harmful effects of potassium depletion. Potassium can be provided conveniently by adding KCl 10 to 20 mEq/L to the regimen.
In the clinical setting of volume overload such as in congestive heart failure, administration of NaCl is clearly inadvisable. Chloride should be repleted with **KCl** as above unless hyperkalemia is present or if the ability to excrete a potassium load is a concern[34, 36].

Intravenous HCl is indicated if NaCl or KCl is contraindicated and correction should be immediate, i.e., when the arterial pH is greater than 7.55, and in the presence of hepatic encephalopathy, cardiac arrhythmia, digitalis cardiotoxicity, or altered mental status. The amount of HCl, given as 0.1 or 0.2 M solutions, needed to correct alkalosis is calculated by the formula:

$0.5\times$Body weight(kg)$\times$Desired decrement in plasma bicarbonate (mEq/L)

continuing losses must also be replaced. The use of 50% of body weight as the volume of distribution of infused protons related mainly to the prior buffering of alkali including those in intracellular sites; infused protons must restore these buffers as well as titrating extracellular bicarbonate. Because the goal of such therapy is to rescue the patient from severe alkalosis, it is usually prudent to plan to initially restore the plasma bicarbonate concentration halfway toward normal. HCl must be given through a catheter placed in the vena cava or a large tributary vein. The proper placement of

the catheter should be confirmed radiographically because leakage of HCl can lead to sloughing of perivascular tissue; in the mediastinum, this could be a catastrophe. Rates of infusion up to 25 mEq/h have been reported. These patients are best managed in an intensive care unit with frequent measurement of arterial blood gases and electrolytes[37].

NH4Cl is an alternative, which may be given into a peripheral vein; its rate of infusion should not exceed 300 mEq/24 h. NH4Cl is contraindicated by the presence of renal or hepatic insufficiency. In concurrent renal failure, azotemia would be worsened and, in hepatic failure, acute ammonia intoxication with coma could result. Lysine or arginine HCl should be avoided because they have been associated with dangerous hyperkalemia. If GFR is adequate (serum creatinine $<$4 mg/dl), the use of acetazolamide 250 to 500 mg daily, which produces a diuresis of primarily NaHCO3 by inhibition of carbonic anhydrase, can be considered. When high sodium excretion must be maintained or if a high serum potassium is present, acetazolamide is particularly useful[36, 38].

Additional therapeutic approaches are needed in certain specific clinical situations associated with chloride-depletion metabolic alkalosis. In the presence of pernicious vomiting or the need for the continual removal of gastric secretions, metabolic alkalosis will continue to be generated and replacement of preexisting deficits will be impeded by these losses. In such circumstances, the administration of a proton pump inhibitor, such as omeprazole, will blunt gastric acid production. Antiemetics may also be helpful. Proton pump inhibitors have also been used effectively to blunt the acid loss that occurs with gastrocystoplasty.

2. **Chloride-Resistant Alkalosis**

When potassium depletion is associated with a mild-to-moderate metabolic alkalosis, oral KCl 40 to 60 mEq four or five times per day usually will suffice for correction. If, however, a cardiac arrhythmia or generalized weakness is

present, intravenous KCl may be given at rates as high as 40 mEq/h in concentrations not to exceed 60 mEq/L. These very high rates should be used only when life-threatening situations are encountered. The patient should be monitored by electrocardiogram and frequent determinations of plasma potassium concentration because muscle uptake of potassium may initially be diminished by downregulation of muscle Na,K-ATPase. Glucose should be omitted initially from the solution used to administer potassium because stimulated insulin secretion may cause plasma potassium concentration to decrease even further. However, once potassium repletion has begun, the presence of glucose in the infusion will facilitate cellular potassium repletion. Because nephropathy due to potassium depletion may impair free water excretion, plasma sodium should be monitored, particularly if hypotonic fluids are administered.

When mineralocorticoid excess is the proximate cause, therapy is directed at either removal of the source or its blockade. Potassium-sparing diuretics, specifically spironolactone with hyperaldosteronism.

Many primary disorders of mineralocorticoid excess are definitively treated by tumor ablation. ACTH-secreting pituitary tumors may be removed by trans-sphenoidal resection or irradiation. With adrenal tumors, adrenalectomy, either unilateral or bilateral as appropriate, may be curative. In the ectopic ACTH syndrome, the ideal treatment of the secreting tumor can rarely be accomplished[36, 39].

III Respiratory Acidosis

Definition:

Primary acid-base disorder in which arterial pCO_2 rises to a level higher than expected[40]

Causes:

Respiratory acidosis may occur due to a variety of etiologies, including the following[41]:

- Chronic obstructive pulmonary disease - Emphysema, severe asthma ,

chronic bronchitis

- Neuromuscular diseases - Amyotrophic lateral sclerosis, diaphragm dysfunction and paralysis, Guillain-Barr syndrome, myasthenia gravis, muscular dystrophy
- Chest wall disorders - Severe kyphoscoliosis; flail chest; less commonly, ankylosing spondylitis, pectus excavatum
- Obesity-hypoventilation syndrome
- Obstructive sleep apnea
- CNS depression - Drugs (eg, narcotics, barbiturates, benzodiazepines, other CNS depressants), neurologic disorders (eg, encephalitis, brainstem disease, trauma), primary alveolar hypoventilation
- Other lung and airway diseases - Laryngeal and tracheal stenosis
- Lung-protective ventilation in ARDS

Clinical effects of Hypercapnia[42]:

- Stimulation of ventilation via both central and peripheral chemoreceptors
- Cerebral vasodilation increasing cerebral blood flow and intracranial pressure
- Stimulation of the sympathetic nervous system resulting in tachycardia, peripheral vasoconstriction and sweating
- Peripheral vasodilation by direct effect on vessels
- Central depression at very high levels of PaCO2

Compensation[16, 43]:

"The compensatory response is a rise in the bicarbonate level"

By application of Henderson Hasselbalch equation

$$pH = pKa + Log_{10}\frac{[HCO3^{-}]}{0.03 \times (PaCO_2)}$$

Bicarbonate level will increase for counteracting the effect of CO2 in pH , this increase of $HCO3^{-}$ has Immediate component which slightly rise HCO_3 and slower component, this slow component is responsible for conversion of an (*acute respiratory acidosis*) to (*chronic respiratory acidosis*).

1. **Compensation in acute respiratory acidosis**
   In acute stage there is insufficient time for the kidney for compensation, the increase in bicarbonate only partially returns the extracellular pH towards normal.

   By application of law of mass action .

   $$CO_2 + H_2O \Longleftrightarrow H_2CO_3 \Longleftrightarrow H^+ + HCO_3^-$$

   Increasing $PaCO_2$ level cause the reaction to shift to the right. In the presence of carbonic anhydrase enzyme, this reaction occurs rapidly in RBCs, the produced hydrogen ion is buffered by protein and phosphate intracellularly and hemoglobin in RBCs, by removal of hydrogen ion, pulls the reaction to the right resulting in an increased bicarbonate production,the bicarbonate exchanges for chloride ion across the erythrocyte membrane and the plasma bicarbonate level rises

   " *Empirically every 10 mm Hg increase of level of*$PaCO_2$ *is associated with increase in bicarbonate level by one mmol/l* "

2. **Compensation in Chronic respiratory acidosis**
   The response occurs because increased arterial $PaCO_2$ increases intracellular CO_2 in proximal tubular cells and this causes increased H secretion from the proximal convoluted tubules cells into the tubular lumen. This results in:

   (a) Increase HCO_3^- production which crosses the basolateral membrane and enters the circulation (so plasma HCO_3^- increases.)

(b) Increase Na+ reabsorption in exchange for H^+ and less in exchange for Cl^- (so plasma [Cl^-] falls)

(c) Increase 'NH3' production to 'buffer' the H^+ in the tubular lumen (so urinary excretion of NH4Cl increases)

.

Studies have shown that an average 5 mmol/l increase in HCO_3^- occurs for every 10 mmHg increase in pCO_2 from the reference value of 40 mmHg

Assessment of respiratory acidosis[44]:

In the absence of another metabolic acid base disturbance using value of 40 mmHg as reference of deviation. However in the presence of other metabolic acid base disturbance expected $PaCO_2$ should be considered as a reference range.
Expected $PaCO_2$ can be calculated using the following formula :

$$HCO_3^- = (\Delta PaCO_2/10)5 + 24(\text{Normal}HCO_3^-)$$

$$HCO_3^- = (\text{Measured}PaCO_2 - 40/10)5 + 24$$

$$HCO_3^- = (\text{Measured}PaCO_2 - 40 + 48/2)$$

$$2 \times HCO_3^- = \text{Measured}PaCO_2 + 8$$

$$\text{Expected PaCO2} = 2 \times (HCO3^-)(\text{admission value}) - 8$$

Correction ”restoration of adequate alveolar ventilation”:

Treatment usually directed to treatment of cause, In sever cases, intubation and mechanical ventilation may be needed to restore alveolar ventilation[16, 42].

IV Respiratory Alkalosis

Definition

Primary acid-base disorder in which arterial PaCO2 falls to a level lower than expected. If there was no compensation and no other acid-base disorder present, then this must necessarily lead to an increase in arterial pH. If there is no metabolic acid-base disorder present, then the actual measured arterial PaCO2 is compared against the standard reference value of 40mmHg .If there is a co-existing metabolic acidosis, then the expected PaCO2 used for comparison is not 40 mmHg but a calculated value which adjusts for the amount of change in arterial PaCO2 which occurs due to respiratory compensation. This decrease in PaCO2 that occurs as compensation for a metabolic acidosis is not a respiratory alkalosis as it is not a primary process. For this reason, hypocapnia is not synonymous with respiratory alkalosis[45].

Causes[46, 47]

The differential diagnosis of respiratory alkalosis is broad; therefore, a thorough history, physical examination, and laboratory evaluation are helpful in limiting the differential and arriving at the diagnosis.

1. Central nervous system causes are as follows:

    - Pain
    - Hyperventilation syndrome
    - Anxiety
    - Psychosis
    - Fever
    - Cerebrovascular accident
    - Meningitis
    - Encephalitis
    - Tumor
    - Trauma

2. Hypoxia-related causes are as follows:
    - High altitude
    - Severe anemia
    - Right-to-left shunts
3. Drug-related causes are as follows:
    - Progesterone
    - Methylxanthines
    - Salicylates
    - Catecholamines
    - Nicotine
4. Endocrine-related causes are as follows:
    - Pregnancy
    - Hyperthyroidism
5. Pulmonary causes are as follows:
    - Pneumothorax/hemothorax
    - Pneumonia
    - Pulmonary edema
    - Pulmonary embolism
    - Aspiration
    - Interstitial lung disease
    - Asthma
    - Emphysema
    - Chronic bronchitis
6. Miscellaneous causes are as follows:
    - Sepsis

- Hepatic failure
- Mechanical ventilation
- Heat exhaustion
- Recovery phase of metabolic acidosis
- Congestive heart failure

Clinical effect of respiratory alkalosis[47, 48]:

1. Neurological effects
   - Increased neuromuscular irritability.
   - Decreased intracranial pressure (secondary to cerebral vasoconstriction)
   - Increased cerebral excitability associated with the combination of hypocapnia & use of enflurane
   - Inhibition of respiratory drive via the central peripheral chemoreceptors
2. Cardiovascular effects
   - Cerebral vasoconstriction (causing decreased cerebral blood flow) [short-term only as adaptation occurs within 4 to 6 hours]
   - Cardiac arrhythmias
   - Decreased myocardial contractility
3. Other effects
   - Shift of the haemoglobin oxygen dissociation curve to the left (impairing peripheral oxygen unloading)
   - Slight fall in plasma [K^+]

Compensation:

"The compensatory response is a fall in bicarbonate level."

1. Compensation in an acute Respiratory Alkalosis[49, 16]

   - **Mechanism:**
     Changes in the physicochemical equilibrium occur due to the lowered PaCO2 and this results in a slight decrease in $HCO3^-$. There is insufficient time for the kidneys to respond so this is the only change in an acute respiratory alkalosis. The buffering is predominantly by protein and occurs intracellularly; this alters the equilibrium position of the bicarbonate system.
   - **Magnitude:**
     There is a drop in $HCO3^-$ by 2 mmol/l for every 10 mmHg decrease in PaCO2 from the reference value of 40 mmHg.
   - **Limit:**
     The lower limit of 'compensation' for this process is 18 mmol/l - so bicarbonate levels below that in an acute respiratory alkalosis indicate a co-existing metabolic acidosis. (Alternatively, there may be some renal compensation if the alkalosis has been present longer than realized.)

2. Compensation in a chronic Respiratory alkalosis

   - **Mechanism:**
     Renal loss of bicarbonate causes a further fall in plasma bicarbonate (in addition to the acute drop due to the physicochemical effect and protein buffering).
   - **Magnitude:**
     Studies have shown an average 5 mmol/l decrease in $[HCO3^-]$ per 10mmHg decrease in PaCO2 from the reference value of 40 mmHg. This maximal response takes 2 to 3 days to reach.
   - **Limit:**
     The limit of compensation is a $[HCO3^-]$ of 12 to 15 mmol/l.

Assessment:[16, 47]

The severity of a respiratory alkalosis is determined by the difference between the actual PaCO2 and the expected PaCO2. The actual PaCO2 is the measured value from the blood gas results.

- In acute respiratory disorder:

$$\Delta pH = 0.008 \times (\Delta PaCO_2)$$

- In chronic respiratory disorder:

$$\Delta pH = 0.003 \times (\Delta PaCO_2)$$

If no metabolic acid-base disorder is present, a PaCO2 of 40 mmHg is taken as the reference point (ie. the expected PaCO2).
If a metabolic disorder is present, respiratory compensation will produce a new reference value of PaCO2 for comparison.

Management of respiratory alkalosis:

"Management of respiratory alkalosis must be directed toward correcting the underlying cause."

Respiratory alkalosis itself, is rarely life threatening, therefore, emergent treatment is usually not indicated unless the pH level is greater than 7.5. Because respiratory alkalosis usually occurs in response to some stimulus, treatment is usually unsuccessful unless the stimulus is controlled.

The tidal volume and respiratory rate may be decreased in mechanically ventilated patients who have respiratory alkalosis. Inadequate sedation and pain control may be the etiology of respiratory alkalosis in patients breathing over the set ventilator rate.

Chapter 2

Development Of Traditional Approach

A Analytic tools used in acid base balance

I Henderson Hasselbalch Equation

1909, Henderson established the term of acid-base balance, he defined this process in the term of carbonic acid equilibrium, work that later was refined by Hasselbalch in 1916, essentially, their method described acid-base balance in terms of the hydration equation for CO2, the only clinical chemistry test available at that time[50].

$$CO_2 + H_2O \Longrightarrow H_2CO_3 \Longrightarrow H^+ + HCO_3^-$$

$$pH = pKa + Log_{10}\frac{HCO_3^-}{H_2CO_3^{-2}}$$

$$TotalCO_2 = (PCO_2) \times 0.03$$

$$by\ substitution$$

$$pH = 6.1 + Log_{10}[\frac{[HCO_3^-]}{(PaCO_2) \times 0.03}] \Longrightarrow \text{Henderson Hasselbalch equation}$$

II Boston Approach "Carbon dioxide bicarbonate approach"

Using mathematical relationships between carbon dioxide tension and serum bicarbonate derived from Henderson Hasselbalch equation, Schwartz and colleagues, at Tufts University in Boston, developed an approach to acid-base

chemistry using number of patients with known acid base disturbances at steady state of compensation

They described six primary states of acid-base imbalance *Figure 2* using liner equation (metabolic acidosis , Acute respiratory acidosis , chronic respiratory acidosis, metabolic alkalosis, acute respiratory alkalosis and chronic respiratory alkalosis[1, 51])

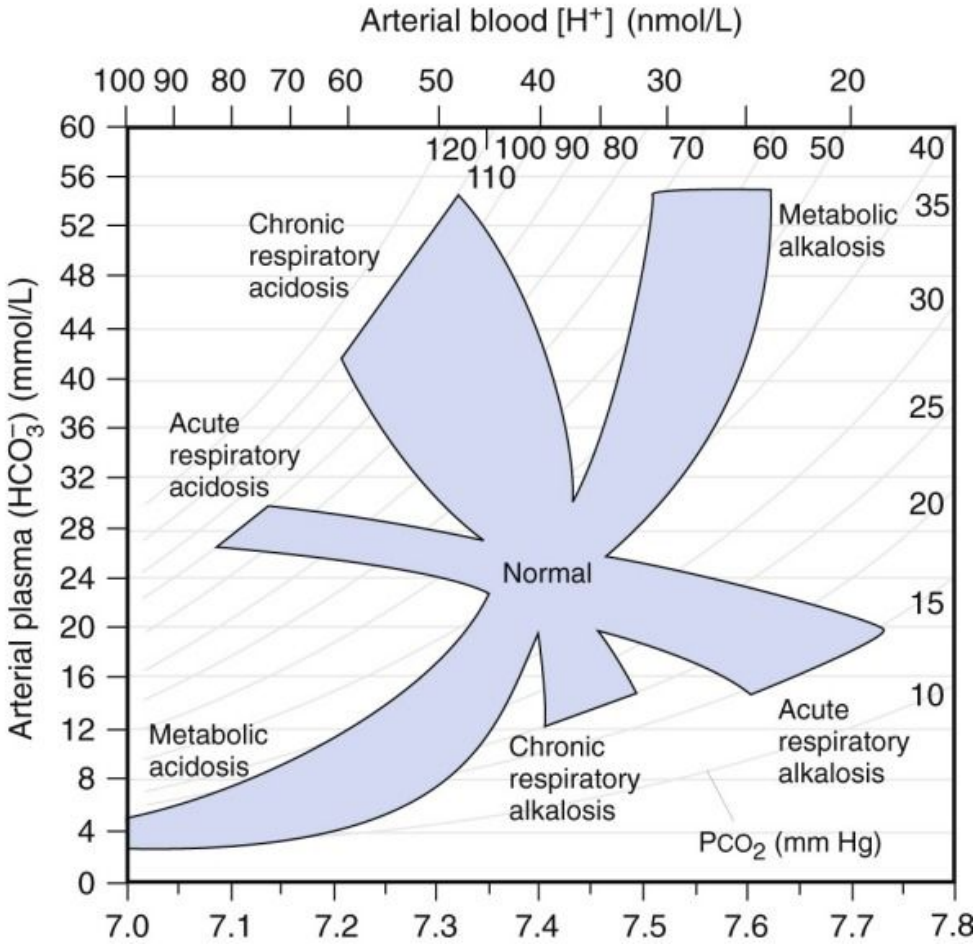

Figure 2: Acid-base nomogram using the Boston approach[1].
Different acid-base disturbances can be distinguished based on the relative values of partial pressure of carbon dioxide (PaCO2) and concentration of bicarbonate ion ([HCO3$^-$]).

III Winter's Rules

Rules established interrelationships among the degree of primary reduction of the metabolic component, the compensatory reduction of the respiratory component, and the resultant reduction of whole blood pH. The rules describe the normal physiological reactions of the human body to one isolated acid-base perturbance

The clinical question the rules are designed to answer in this situation is, whether the patient's respiratory compensation is within the range to be expected or whether there is an additional component of respiratory disturbance, too, e.g. impending respiratory failure.

The origin of rules can be traced to a study published in 1967[52]. The study leads to the formula:

$$PaCO_2\ (mmHg) = 1.54 \times [HCO_3^-]\ (in\ mmol/l) + 8.36,\ with\ a\ standard\ error:\ S.E. = 1.11\ mmHg$$

This has been simplified to the now widely known formula:

$$PaCO_2\ (in\ mmHg) = 1.5 \times [HCO_3^-]\ (in\ mmol/l) + 8$$

Brandis published bed side rules for assessment of compensation [53]:

1. **Rule 1 : The "1 for 10" rule for Acute Respiratory Acidosis**
   The [HCO3$^-$] will increase by 1 mmol/l for every 10 mmHg elevation in PaCO2 above 40 mmHg.

   $$Expected\ [HCO3^-] = 24 + \ (Actual\ PaCO2\ -\ 40)\ /\ 10$$

2. **Rule 2 : The "4 for 10" rule for Chronic Respiratory Acidosis**
   The [HCO3] will increase by 4 mmol/l for every 10 mmHg elevation in PaCO2 above 40m mHg.

   $$Expected\ [HCO3^-] = 24 + 4 \times \ (Actual\ PaCO2\ -\ 40)\ /\ 10$$

3. **Rule 3 : The "2 for 10" rule for Acute Respiratory Alkalosis**
   The [HCO3] will decrease by 2 mmol/l for every 10 mmHg decrease in PaCO2 below 40 mmHg.

$$Expected\ [HCO3^-] = 24 - 2 \times (40 - Actual\ PaCO2) / 10$$

4. **Rule 4 : The "5 for 10" rule for a Chronic Respiratory Alkalosis**
   The [HCO3] will decrease by 5 mmol/l for every 10 mmHg decrease in PaCO2 below 40 mmHg.

$$Expected\ [HCO3^-] = 24 - 5 \times (40 - Actual\ PaCO2) / 10 \quad (range: +/- 2)$$

5. **Rule 5 : "The One & a Half plus 8" rule - for a Metabolic Acidosis**
   The expected PaCO2 (mmHg) is calculated from the following formula:

$$Expected\ PaCO2 = 1.5 \times [HCO3^-] + 8\ (range: +/- 2)$$

6. **Rule 6 : "The Point Seven plus Twenty" rule - for a Metabolic Alkalosis**
   The expected PaCO2(mmHg) is calculated from the following formula:

$$Expected\ PaCO2 = 0.7 \times [HCO3]^- + 20\ (range: +/- 5)$$

IV Copenhagen Approach

Development

Henderson wrote the law of mass action for carbonate species (the Henderson equation) as

$$H = K'1 \times (CO2/HCO3)$$

Where:

- CO2 is the total concentration of dissolved CO2 gas and aquas H2CO3 in plasma,
- H^+ and $HCO3^-$ are concentration of hydronium and bicarbonate in plasma , and k'_1 is the equilibrium constant for associated reaction

Later Hasselbalch represented the Henderson equation in logarithmic pH form (Henderson Hasselbalch equation)

$$pH = pK'1 + log(HCO3/[S_{CO2} \times PaCO2])$$

S_{CO2} is the solubility coefficient of CO2 in plasma

Henderson persuaded his friend Van Slyke to place that equation on quantitative footing, Van slyke realized that the plot of log PaCO2 Vs Plasma pH was liner *(Figure 3)* in the first approximation so that PaCO2 could be easily obtained by :

$$LogPaCO2 = -pH + Log[(HCO3^{-})/K_1' \times S_{CO2}$$

By adding known amount of acid or base and reading value of pH vs log PaCO2,

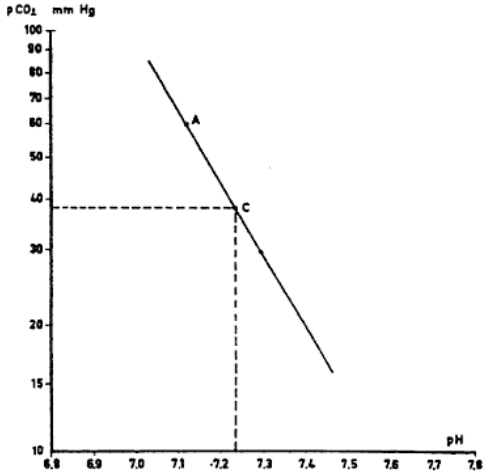

Figure 3: The pH of the unequilibrated blood can be located on the line to give the patient's PaCO2[50].
The slope of the line is related to the buffering capacity of the blood. A 45 angle is the line describing the Hndersson-Hasselbalch equation Applied to the bicarbonate-carbonic acid system. A steeper line indicates greater buffering.

A line of "non respiratory pH" could be obtained (*Figure 4*) which was known as *base excess*[50, 54, 55]

The "base excess" is determined by reading the value at the intersection of the patient's pH vs log PaCO2 line and the base excess curve of the nomogram.The "base excess" was derived by Astrup by drawing the curve obtained by adding known amounts of acid or base to a normal blood sample *(Figure 5)*

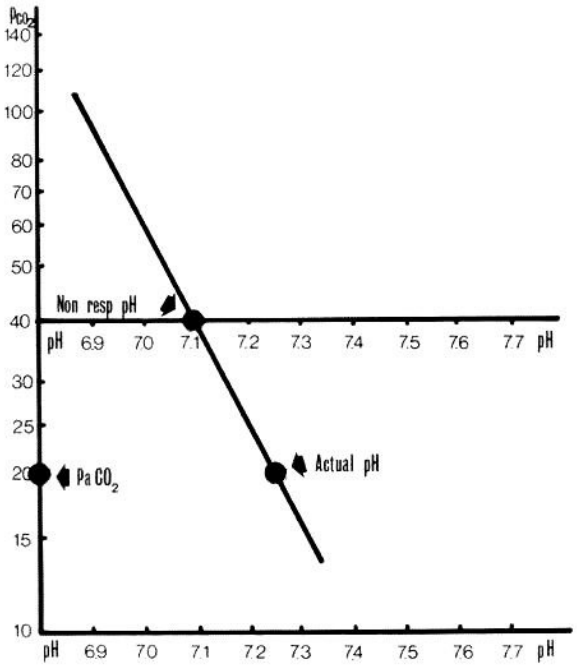

Figure 4: Non-respiratory pH. a pH/PaCO2 line has been plotted and the actual pH marked[55].
Non-respiratory pH is where the pH/PaCO2 line crosses the PaCO2=40 mmHg line. In this case it is 7.1

Principles of Interpretation:

Examination of the Astrup nomogram reveals that in almost every case there is both a respiratory and metabolic component. Each must be analyzed separately. A new definition of terms was possible as the following :

- Respiratory acidosis: PaCO2 above 45 mm of mercury.
- Respiratory alkalosis: PaCO2 below 35 mm of mercury.
- Metabolic acidosis: Base excess below -3 mEq per liter.
- Metabolic alkalosis: Base excess above + 3 mEq per liter

The slope of Astrup curve depends on the buffer capacity of the blood , when fixed acid is added to blood sample the curve is displaced to the left , when the base is added the curve is displaced to the right

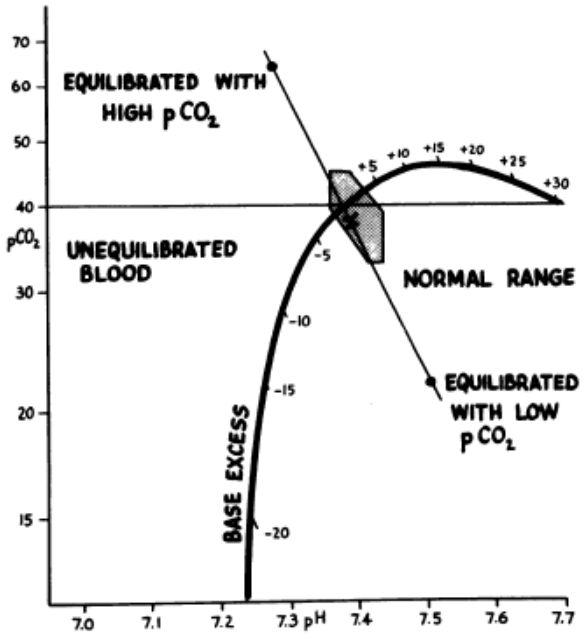

Figure 5: Astrup nomogram. Points of equilibration of blood with known CO-O2 gas mixtures define the line[56].
The pH of the unequilibrated blood sample was 7.39.The PaCO2 read from the nomogram was 38 mmHg.The shaded polygon is the normal range

Asturp became aware that acid base status of the organism is determined by the following quantities :

- The actual pH of the arterial blood
- The actual PaCO2 of arterial blood "representing the respiratory component"
- The quantity that represent the non respiratory factors

By equilibrating temperature controlled oxygen-CO2 gas mixture with separated plasma or anti coagulated fully oxygenated whole blood he reproduced faithfully Van Slayke's buffer line
Asturp preferred the "standard bicarbonate" as bicarbonate concentration of the plasma that had been equilibrated to PaCO2=40 mmHg. He found that intercept of pH/LogPaCO2 line could be displaced by addition of strong acid or strong base, creating base excess or deficit[50, 55]

Daneil[56]introduced examples of cases with different acid base disorders (metabolic and respiratory in origin) using Asturp Nomogram *(Figure 6)*:

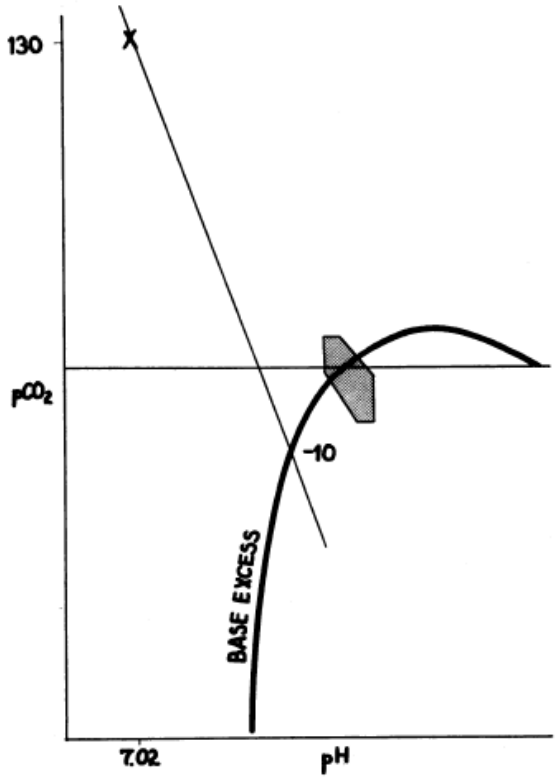

Figure 6: Case for respiratory obstruction of 7 year old girl who operated on a lacerated bronchus[56]

Case for respiratory obstruction of 7 year old girl who operated on a lacerated bronchus, during the operation it was noted that her respiration was rapid and her color was poor, her pH was 7.02 and CO2 was 130 mmHg, the analysis using nomogram showing that was metabolic element included (Base excess was -10) may be caused by trauma or preoperative dehydration, therapy was directed to shortening the air way (too much dead space was in the anesthesia airway)

Salicylate toxicity case *(Figure 7)* :
5-year-old child was seen a few hours following ingestion of 13 aspirin tablets. Therapy consisted of 50 mEq sodium lactate. The acidifying effects of the

aspirin were completely reversed by lactate therapy, although the central nervous stimulation continued

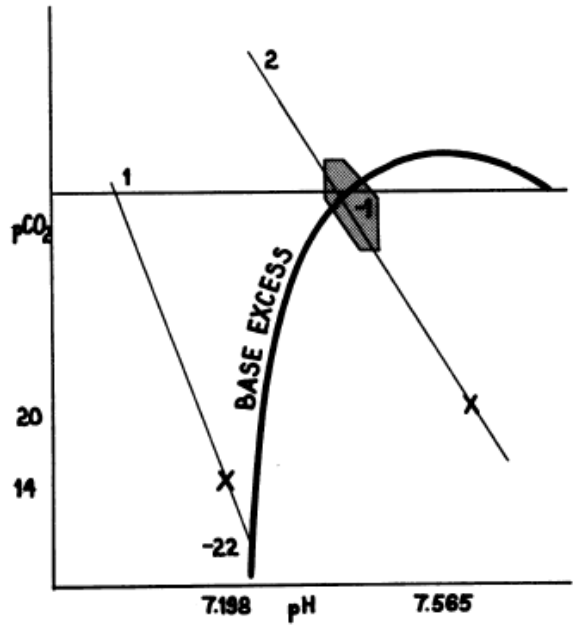

Figure 7: 5-year-old child was seen a few hours following ingestion of 13 aspirin tablets[56]

So **Base excess** could be defined as

"The miliequivalents of strong acid or bases that is needed to titrate one liters (in vitro) of blood or plasma that has been equlibrated to $PaCO2 = 40$ mmHg and to physiological pH of 7.4,at temperature 37 ° C and full O_2 saturation"

Buffer Base

1948, Singer and Hasting proposed buffer base as sum of all blood buffers (anions) including bicarbonate, proteins, and hemoglobin in one liter of blood[57] The slope of buffer line depends on experimental condition including :

- Concentration and oxygen saturation of hemoglobin
- Concentration of protein

- Salinity of sample
- Temperature of plasma

Siggard andersen nomogram

In 1960, Ole Siggard Anderson 25 year old, rotating intern, helped to produce an alignment nomogram relating PaCO2 and pH to base Excess[50, 58] *(Figure 8)*

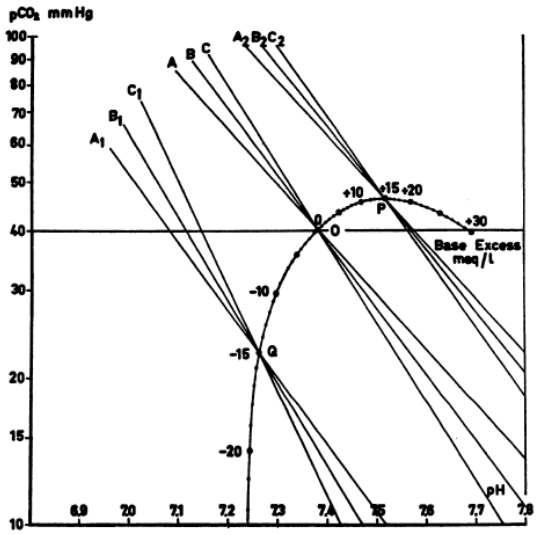

Figure 8: Construction of base-excess curve[55]

- A, B & C are pH/Log CO2 lines.
- A is blood with no hemoglobin, i.e. plasma
- B has a hemoglobin level 10g/100ml
- C a hemoglobin of 20g/100mls.
- A1, B1 C1 are the same lines after adding 15 mEq acetic acid
- A2, B2 and C2 after adding 15 mEq sodium carbonate.
- The points of intersection of A, B and C for each quantity of acid or base added defines points on the base-excess curve

By arrangement of Astrup work and shifting of curve according to change of acid or base and "buffer base" concepts, Siggard Anderson drew his nanogram as the following (Figure 9):

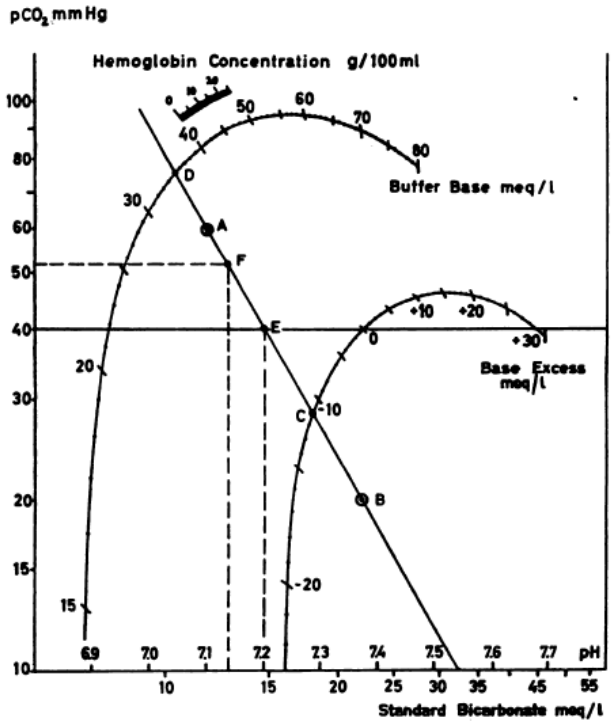

Figure 9: Base excess and Buffer Base lines[55]

- Point A : measured pH at high PaCO2.
- Point B : measured pH at low PaCO2.
- Point F : actual pH of the anaerobically drawn blood and allows the calculation of the actual PaCO2.
- Point C : the BE "Base Excess".
- Point D : the Buffer Base.

By using the previous informations Siggard Anderson produced formula for calculating BE as re-expression of data and called it "Van Slyke equation"

$$BE = (HCO3 - 24.4 + [2.3(Hb) + 7.7][pH - 7.4]) \times (1 - 0.023 \times (Hb))$$

Where $HCO3^-$ and hemoglobin (Hb) are expressed in mmol/L. However, there is great variability in the equations used for calculating BE. While BE is quite accurate in vitro, inaccuracy has always been a problem when applied in vivo in that BE changes slightly with changes in PaCO2 This effect is understood to be due to equilibration across the entire extracellular fluid space (whole blood plus interstitial fluid). Thus, the BE equation was modied to standardize the effect of hemoglobin(Hb = 5 g/dl) on CO2 titration in order to improve the accuracy of the BE in vivo.
The term standard base excess (SBE) has been given to this variable, which better quantifies the change in metabolic acid-base status in vivo[59]

$$SBE = 0.9287 \times (HCO3 - 24.4 + 14.83 \times ([pH - 7.4]))$$

V The Great Transatlantic Debate

1963 , Relman anad shchwatz, in New England Journal Of Medicine presented three major criticisms at base excess :

1. The carbon dioxide titration curve difference between in vivo and in vitro as difference between blood space and volume of distribution of bicarbonate
2. The Copenhagen approach cannot distinguish between primary metabolic disorder and secondary physiological compensation
3. Base excess is not needed as it provided no information that cannot already be gained from clinical institution

The *Copenhagen school* responded by defining SBE which assumes a hemoglobin concentration approximately gg/dl to compensate for bicarbonate relatively large apparent volume of distribution. They substituted the anti-caoagulant heparin for sodium floride for standardization of salinity and they acknowledged that interpretation of base excess dependes upon physiological compensation[60, 61, 62].

B Interpretation of acid base disturbance using Base Excess Concept using Computing Method

Alan W. Grogono, created java applet for interpretation of acid base disorder using pH, PaCO2 and SBE In his diagram he used diagnostic zones, which determine the choice of adjective to describe the magnitude of the respiratory and metabolic components[63] *(Figure 10)*

- Acute Respiratory Acidosis (7 & 8)
- Chronic Respiratory Acidosis (5)
- Metabolic Alkalosis (3)
- Acute Respiratory Alkalosis (18 & 19)
- Chronic Respiratory Alkalosis (16)
- Metabolic Acidosis (14)

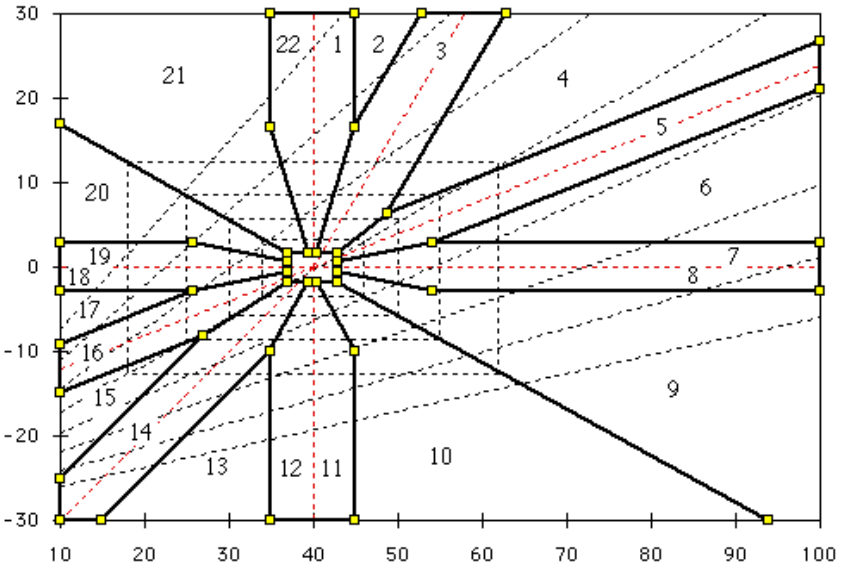

Figure 10: Diagnostic zones of different acid base disorders[63]

Chapter 3

Structured Approach To Assessment Of Acid Base Disturbance Using Traditional Methods

A Boston school, Winter rules and anion gap

1. Anticipate the acid base disturbance from the causes and history that may have effect.
2. Check pH, PaCO2, HCO3, If one of these are abnormal :
3. Check pH
   (a) If pH less than 7.4, the primary disorder is acidosis
   (b) If pH more than or equal 7.4, The primary disorder is alkalosis
4. Metabolic Or Respiratory
   (a) If $HCO3^{-}$ is responsible for changing the pH , the cause is Metabolic
   (b) If PaCO2 is responsible for changing pH, the cause is Respiratory
5. Check pH acceptance (pH range from 7.3 to 7.5):
   (a) In respiratory disorder
      - If pH is accepted, it is chronic respiratory disorder
      - If pH is Unaccepted, it is acute respiratory disorder
   (b) In metabolic disorder
      - Accepted pH , indicates compensated metabolic disorder

- Unaccepted pH, without change in PaCO2 indicates uncompensated metabolic disorder
- Unaccepted pH, with change in PaCO2 indicates partially compensated metabolic disorder

6. Check appropriateness using winter rules (for diagnosis of Mixed disorder , if change is inappropriate that indicates presence of mixed disorder)
7. Further analysis for specific disorders:
   (a) In Metabolic acidosis, calculate Anion Gap:

$$Adjusted\ anion\ gap = 2.5\times[4.5\text{-}measured\ albumin(g/dL)]+observed\ anion\ gap$$

   i. Normal anion gap indicates that acidosis is caused by much chloride
   ii. High anion gap indicates that there are other unmeasured anions
   - Check serum lactate -if more than 2, lactic acidosis may be the cause. Elevated serum lactate can be explained by
     - Type A : circulatory insufficiency as: shock, hypovolemia, oliguria, underresuscitation, anemia, carbon monoxide poisoning, and seizures
     - Type B : biguanides, fructose, sorbitol, nitroprusside, ethylene glycol, cancer, and liver disease
   - Check creatinine and urine output: renal impairment cause increase of renal acids
   - Check blood glucose and urinary ketones : if patient is hyperglycemic and ketotic, Diabetic ketoacidosis may be the cause
   - If patient is ketotic and normoglycemic this is either alcoholic (check blood alcohol) or starvation ketosis
   - If all of these tests are negative, think of intoxication Check toxicology laboratory tests and serum osmolarity

   (b) In metabolic alkalosis, check chloride in urine :
   Either it will be chloride responsive or chloride resistant[1, 44, 52, 59].

B Base Excess

1. Step 1. Look at the pH (three possibilities):
   (a) <7.35 acidosis
   (b) 7.35-7.45 normal or compensated acidosis
   (c) >7.45 alkalosis
2. Step 2. Look for respiratory component (volatile acid = CO2):
   (a) PaCO2 <35 mm Hg respiratory alkalosis or compensation for metabolic acidosis
   (b) PaCO2 35-45 mm Hg normal range
   (c) PaCO2 >45 mm Hg respiratory acidosis (acute if pH <7.35, chronic if pH in normal range)
3. Step 3. Look for a metabolic component (i.e., buffer base utilization):
   (a) BD >-5 metabolic acidosis
   (b) BE -5 to +5 normal range
   (c) BE >5 alkalosis

   Put this information together. Options:

   (a) Acidosis, CO2 <35 mm Hg, ± BD >-5 acute metabolic acidosis
   (b) Normal range pH CO2 <35, BD >-5 acute metabolic acidosis plus compensation
   (c) Acidosis, PaCO2 >45 mm Hg, normal range BE acute respiratory acidosis
   (d) Normal range pH, PaCO2 >45 mm Hg, BE >+5 prolonged respiratory acidosis
   (e) Alkalosis, PaCO2 >45 mm Hg, BE >+5 metabolic alkalosis
   (f) Alkalosis, PaCO2 <35 mm Hg, BDE normal range, acute respiratory alkalosis
   (g) If the acid-base picture does not conform to any of these, a mixed picture is present[1, 59].

Chapter 4

Quantitative Approach for interpretation of acid base balance Approach

A Stewart definitions for acid and base

- **Neutral Solution :** solution that its hydrogen ion concentration is equal to hydroxyl ion concentration.
- **Acidic Solution :** solution that its hydrogen ion concentration is greater than hydroxyl ion concentration.
- **Alkaline Solution :**solution that its hydroxyl ion concentration is greater than its hydrogen ion concentration .
- **Acidic Substance :** substance, if added to solution, it brings about an increase in hydrogen ion concentration of solution, provided all other independent variables in solution remains constant.
- **Base Substance :** substance, if added to solution, it brings about an decrease in hydrogen ion concentration of solution,provided all other independent variables in solution remains constant.
- **Ions, nonelectrolytes, strong and weak electrolytes:**
  When a substance dissolves in water, it will dissociate into charged particles called ions, the process of going into solution in water is more than a simple physical process. Substance that dissociate to form ions are called electrolytes, which subdivided into two classes, strong and weak. Substances that do not dissociate are called non-electrolytes, and they have

little interest in acid base chemistry except if they have effect in water concentration (osmolarity) or alter the value of parameters such as dissociation constant.

- **Strong electrolytes :** electrolytes which are completely dissociated in solution,i.e parent substance disappears when dissolved in water For example, NaCl if dissolved in water, solution will contain Na^+, Cl^+, H^+, OH^+, water and no NaCl molecules

- **Weak electrolytes:** substance that partially dissociate when dissolved in water, i.e the molecules of parent substance as well as the product of dissociation will exist For example, taking [HA] as prototype weak electrolyte, for writing reaction it will be

$$[HA] \Longleftrightarrow [H^+] + A^-$$

For achieving equilibrium,

$$\textit{"The rate of dissociation should equal rate of recombination"}$$

$$[H^+][A^-] = K_A \times [HA]$$

$$K_A \textit{ is dissociation constant}$$

- **Independent variables :** the variables being manipulated or changed by external maneuvers.

- **Dependent variables :** observed result of the independent variable being manipulated.

- **Strong Ion Difference (SID):** the sum of all strong base cation concentration minus the sum of all strong anion concentrations, all expressed in equivalents per liter.

- **Conversion of mass:** the amount of each component substance in any aqueous solution remains constant unless substance is added or removed from solution and substance that is generated or destroyed by chemical reaction within the solution .

- **Quadratic equation :** polynomial equation of the second degree. The general form is :

$$ax^2 + b^x + c = 0$$

A quadratic equation has two solutions, called roots. These two solutions may or may not be distinct, and they may or may not be real. The roots are given by the quadratic formula:

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

- **Cubic function :** is a function of the form

$$f(x) = ax^3 + bx^2 + cx + d$$

Where "a" is nonzero; or in other words, a polynomial of degree three. The derivative of a cubic function is a quadratic function. The integral of a cubic function is a quartic function.[64, 65]

B Mathematical Concept Of Stewart Approach

I The Simplest Acid-Base System : Pure water

1985, in his book, Stewart introduced his different vision on acid base balance. Presentation of "The Simplest Acid-Base System : Pure water" model was done as the following [66]:
Water dissociates into hydrogen and hydroxyl ions. At 37 ° C, the dissociation constant is 4.3×10^{-16} Eq/Liters. It could be described as :

$$[H_2O] \Longleftrightarrow H^+ + OH^-$$

That is very fast reaction in either direction, and complete equilibrium may always be assumed in biological situations. The quantitative requirement of three component substance at equilibrium is

$$[H^+]\text{x}[OH^-] = K_W \times [H_2O]$$

As K_W is highly temperature dependent and very small, the dissociation

process has no significant effect on water concentration. So, $[H_2O]$ can be considered constant and by combination to K_W into new constant, K'_W,called the ionic product of water

$$K'_W = K_W \times [H_2O]$$

By substitution

$$[H^+] \times [OH^-] = K'_W$$

Since water contains Hydrogen and Hydroxyl only

$$H^+ - OH^- = 0$$

So it is easy to determine that

$$H^+ = OH^-$$

And

$$[H^+] \times [H^+] = K'_W$$
$$[H^+] = \sqrt{K'_W}$$
$$[OH] = \sqrt{K'_W}$$

The following definitions were introduced :

1. Solution is acid-base neutral if the hydrogen ion concentration is equal to the square root of the K'_W.
2. A solution is acidic if [H^+] $> \sqrt{(K'_W)}$
3. A solution is basic if [H^+] $< \sqrt{(K'_W)}$

The term "Strong ions and Strong Ion Difference" was explained by the following example[67]:
Adding specified amount of NaCl to Water [H2O], so solution will only contain Na^+,Cl^-,H^+ And OH^- By application of electrical neutrality:

$$Na^+ - Cl^- + H^+ - OH^- = 0$$

$$[H]\text{x}[OH] = K'_W$$

By substitution of OH^- by $[K'_W]/[H]$

$$H^+ - (K'_W/H^+) + Na^+ - Cl^- = 0$$

By multiplying the previous equation by H^+ and rearrangement

$$[H+]^2 + [H^+]([Na^+] - [Cl^-]) - K'_W = 0$$

the quadratic equation can by solved as

$$[H^+] = \frac{-([Na^+] - [Cl^-])}{2} + \sqrt{(([Na^+] - [Cl^-])^2/4 + K'_W)}$$

By replacing Na^+ and Cl^- by any strong ions, H^+ can be obtained. As the only matter considering strong ions in previous equation is difference between them , so that difference can be expressed as "Strong Ion Difference" [SID]

$$[H^+] = \sqrt{(K'_W + SID^2/4)} - SID/2$$

And by application to OH^-

$$[OH^-] = \sqrt{(K'_W + SID^2/4)} + SID/2$$

So, the Strong Ion difference can be defined as :

"The sum of all strong base cation concentration minus the sum of all strong anion concentration, all expressed in equivalents per Liter."

$$SID = (\sum StrongBaseCation) - (\sum StrongAcidAnions)$$

Similarly given the strong ion composition of any solution that contains only strong electrolytes, H^+ and OH^- can be calculated

Negative value of individual ion concentrations have no physical meaning but the value of SID may be negative, positive, or zero , depending on the excess amount of anion or cations. In biological solution, SID is almost positive. it is on the order of +40 mEq/Liter.In extracellular fluids, Na^+ and Cl^- are the main Strong Ions , the SID is closely to (Na^+ - Cl^-). Graphical representation of relationship between SID and H^+ or OH^- could be demonstrated on *(Figure 11)*

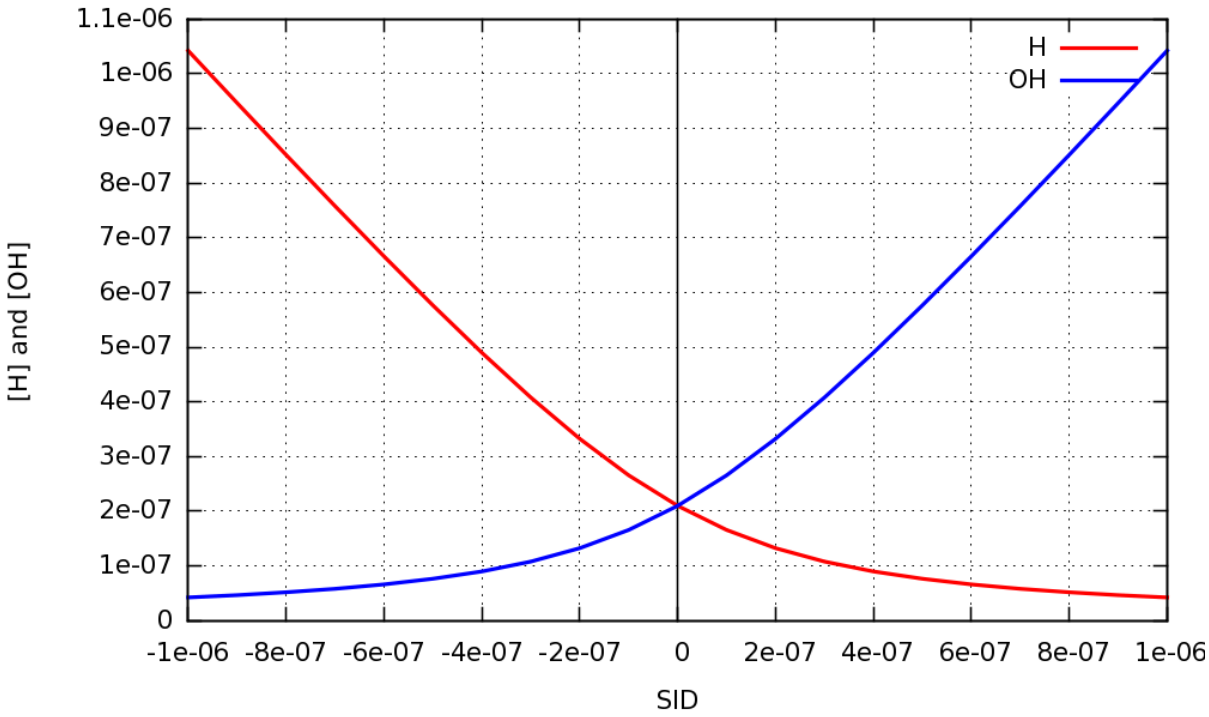

Figure 11: H and OH versus SID with SID value is smaller than 10^{-6} Eq/L[67]

From the Figure 11 :

- **Small SID value :** neutral salt solution
  small SID value means values close to K'_W, using that criterion, when SID is small and is negative left side of curve , H^+ is always larger than OH^-, H^+ varies linearly with SID once SID value is above $10-7$ Eq/Liter, while OH varies in curvilinear fashion, and appears to asymptote toward zero as SID increasingly negative
- **When SID = 0** , that is neutral salt solution, H^+=OH^-=K'W then H and OH curves intersect at SID=0.
- **When SID is positive**, OH^- is larger than H^+, i.e strong base more than strong acid, OH varies linearly with SID once SID is more than 10^{-7} Eq/Liter where H^+ varies non linear

As general rule:

"Whenever [SID] changes in the negative direction (more strong acid or less strong base), then [H^+] increases and [OH^+] decreases. Whenever [SID] changes in the more positive direction, [OH^-] increases and [H^+] decreases. It is also noteworthy that when [SID] is positive, the change in [H^+] is always much less than the change in [SID]"

- **SID negative and larger than 10^{-6} Eq/Liter**, When excess of strong acid anions over strong base cation is larger than 10^{-6} equation:

$$[H^+] = \sqrt{(K'_W + SID^2/4)} - SID/2$$

could be simplified to

$$H^+ = -SID$$

And OH^- will be close to zero so

$$OH^- = K'_W/[-SID]$$

Under this condition "of excess strong acid", H^+ is independent to K'W , but OH^- depends directly on it. When SID is positive the following equations could be concluded

$$OH^- = -SID$$

And H^+ will be close to zero so

$$H^+ = K'_W/-SID$$

And as same above OH^+ is independent to K'_W but H^+ depends directly on it.

Fink O.T. In his website[68] published simple summery for Stewart approach mathematical concept of strong ion difference with comparison to traditional approach for explanation of some body processes and chemical reactions:

Adding HCL to Water :

- **Traditional approach :** adding H^+ will cause increase of H^+ that means acidosis
- **Stewart approach :** *"You are adding a strong anion (Cl^-) without adding a strong cation. Therefore the SID decreases. This is a net negative change in charge due to SID. To maintain electroneutrality, the solution must liberate H^+, leading to acidosis. In the Stewart view, you dont attempt to directly follow the H^+ that you add. At first this may seem convoluted ("I added HCl and [H^+] increased. Why make it more complicated?"). However, the apparent simplicity of the traditional view breaks down when one asks by how much did [H^+] change? When, after adding HCl you measure [H^+], it is immediately apparent that [H^+] does not change in an easily predictable way (as does [Cl^-]. This is because there are many factors that will influence what exactly happens to the added H^+. In mathematical terms, [H^+] is a dependent variable and depends on many factors. SID, on the other hand, is an independent variable."*

Production of stomach acid.

- **Traditional approach:** Parietal cells secrete HCl into the stomach fluid, increasing its acidity.
- **Stewart approach:** *"Parietal cells transport a strong anion (Cl^-) from the plasma into the stomach fluid without transporting a strong cation. This decreases the SID in the stomach fluid, which causes it to be more acidic. To maintain electroneutrality, either a positive charge must move with the Cl^- or a negative charge must move opposite it. This means that either H^+ moves with the Cl^-, or that OH^- or $HCO3^-$ move opposite Cl^- from the stomach acid into the plasma. Which of these occurs is unimportant, and in fact can often not be experimentally determined (exchanging OH^- for Cl^- is indistinguishable from secreting both Cl^- and H^+). The only important fact is that parietal cells decrease the stomach fluid SID by secreting a strong anion and excluding concomitant movement of a strong cation".*

II Effect of adding weak electrolytes

Weak Electrolytes: Weak acid solution contains molecular species [HA] and [A^-]. [HA] and A^- must follow the requirements of dissociation equilibrium and low of mass for A^-. These requirements plus water dissociation equilibrium and electrical neutrality, allowed Stewart to write equations to describe the relationship between four unknown dependent variables "$[H^+], [OH^-], [HA], [A^-]$" and two externally controlled, independent variables "$[SID]$and total acid, $[A_{TOT}]$"[69].

Weak acid dissociation

$$HA \Longleftrightarrow H^+ + A^-$$

Water dissociation

$$[H^+]\text{x}[OH^-] = K'_W$$

Weak acid dissociation

$$[H^+]\text{x}[A^-] = K_A \times [HA]$$

Weak acid conversion

$$[HA] + [A^-] = [A_{TOT}]$$

For achieving electrical neutrality

$$[H^+] + [OH^-] + [SID] + [A^-] = 0$$

By substituting and clearing

$$[H+]^3 + K_A + [SID] \times [H^+]^2 + K_A \times ([SID] - [A_{TOT}]) - K'_W \times [H^+] - K_A \times K'_W = 0$$

By using computer, H^+ value could be get from the previous equation. After plotting the relationship between SID and H^+ in the presence and absence of $[A_{TOT}]$,the following could be concluded *(figures 12 , 13)*

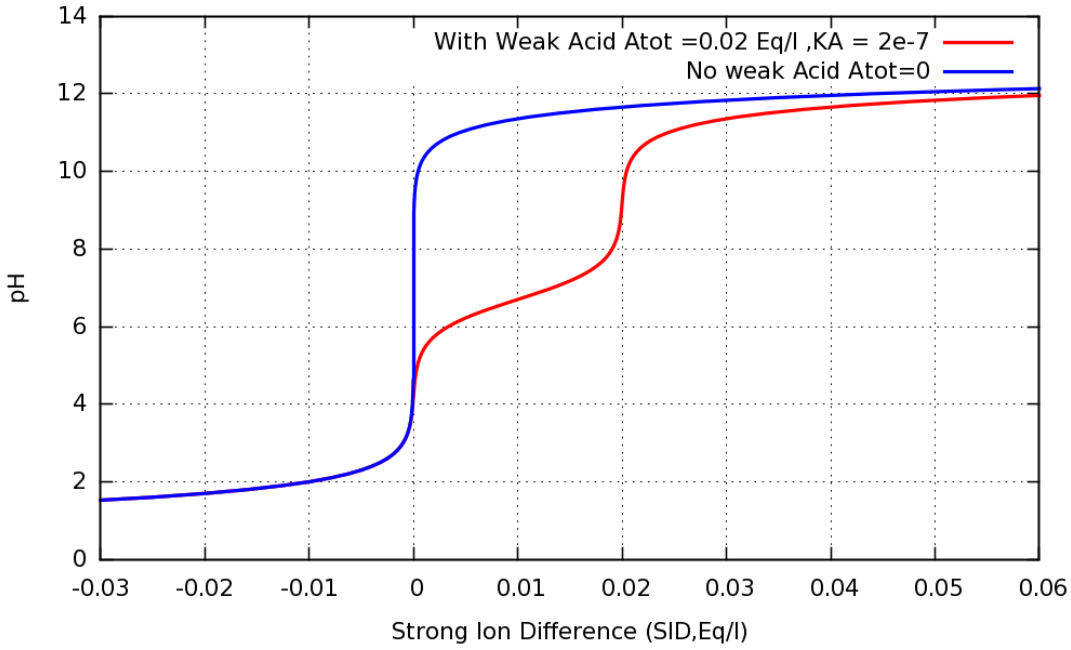

Figure 12: pH is plotted against SID in the presence and absence of A_{TOT}[69]

Blue graph is representing the relationship between SID and pH in absence of weak acid while Red graph is representing the relationship between SID and pH in the presence of $[A_{TOT}]$. $[A_{TOT}]$ only really has an effect between an SID of zero and an SID of about 0.02

- Weak acid is important where SID is between zero and $[A_{TOT}]$
- When [SID] is negative, then $[A^-]$ becomes tiny, and so $[H^+]$ approximates [-SID].
- with [SID] $> [A_{TOT}]$, OH- have to fill the gap between the two (for $[A^-]$ can't of course exceed $[A_{TOT}]$), so $[OH^-] = [SID] - [A_{TOT}]$
- Inside this range of 0 to $[A_{TOT}]$, hydrogen ion concentration changes more rapidly with [SID] than is the case where no weak acid is present Hydrogen ion concentration changes more rapidly in the absence of $[A_{TOT}]$ *(Figure 13)*

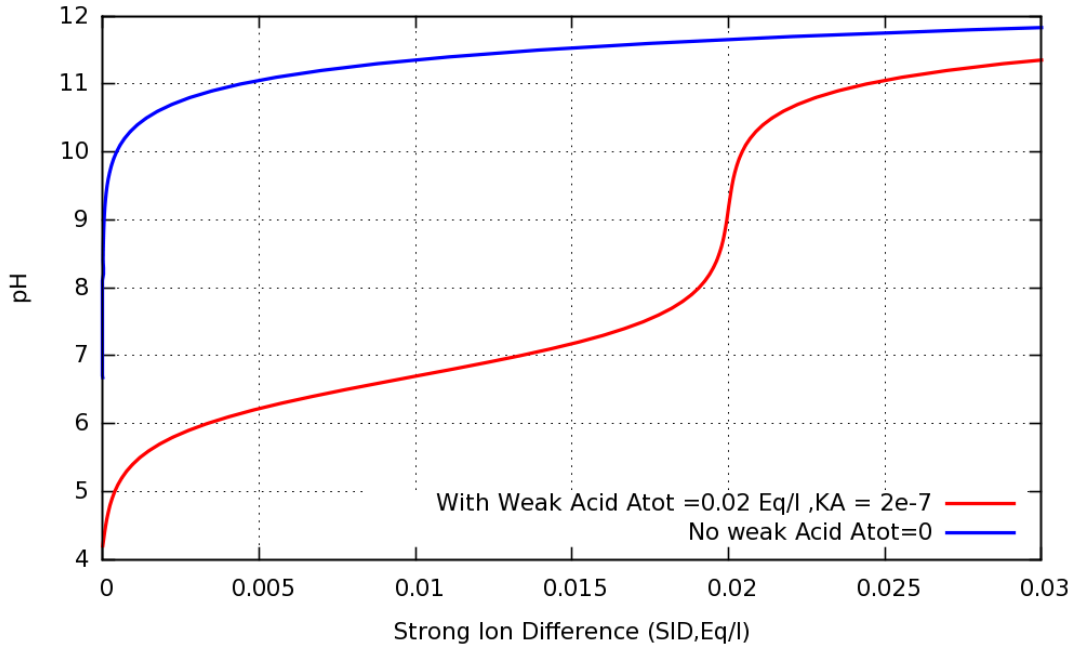

Figure 13: pH is plotted against SID in the presence and absence of A_{TOT}[69]

III Strong Ions plus carbon dioxide

Stewart presented relationship between Strong Ions plus Carbon Dioxide in isolated Intact interstitial fluid[70]; on exposure of solution to CO2 gas , four things may happen, it can dissolve, react with water to form carbonic acid, or even form bicarbonate or carbonate ions.

1. CO2 can Dissolve

$$CO2_{(gas)} \Longleftrightarrow CO2_{(dissolved)}$$

Forward reaction (from gas to dissolved form) is depending on Partial Pressure of CO2 rate of forward reaction (left to right) can be expressed as

$$\text{Rate of forward reaction} = K_{LR} \times PaCO2$$

The reverse reaction (from dissolved to gas form) is depending on concentration of dissolved gas, CO2 rate of reverse reaction(right to left) can be expressed as

$$\text{Rate of reverse reaction} = K_{RL} \times [CO2_{(dissolved)}]$$

By application of low of mass action, on equilibrium:

$$K_{LR} \times PC_{(g)} = K_{RL} \times CO2_{Dissolved}$$

$$PC_{(g)} \textit{ as symbol for partial pressure } CO2 \textit{ in gas form}$$

$$CO2_{Dissolved} = PC_{(g)} \times (K_{LR}/K_{RL})$$

$$CO2_{Dissolved} = Sc \times PC_{(g)}$$

$$Sc \textit{ is replacement of } (K_{LR}/K_{RL}) \textit{ and it represents the solubility coefficient of } CO2 \textit{ or Henry's law constant}$$

2. Carbon Dioxide reaction in water
   Dissolved CO2 could be removed from solution by the following two reactions which will lead to same result, CO2 can combine with water to form H2CO3 (Carbonic acid). This molecule can dissociate to form H^+ and HCO3. CO2 can combine to OH ions to form $HCO3^-$ directly :

$$CO_2 + H_2O \Longleftrightarrow H_2CO_3$$

$$[CO2_{(dissolved)}] \times [H_2O] = K \times [H_2CO_3]$$

   By treating H2O as constant

$$[H_2CO_3] = K_H \times PCO_2$$

   It is common practice to neglect H2CO3 as its concentration is small compared to Dissolved CO2
   By dissociation of H_2CO_3

$$H_2CO_3 \Longleftrightarrow H^+ + HCO_3^-$$

   Equilibrium is represented by

$$[H^+] \times [HCO_3^-] = K \times [H_2CO_3]$$

$$[H^+] \times [HCO_3^-] = K_C \times P_C$$

Once formed, HCO3$^-$ may rapidly dissociate:

$$HCO_3^- \Longleftrightarrow H^+ + CO3^{-2}$$

Equilibrium is represented by:

$$[H^+] \times [CO3^{-2}] = K_3 \times [HCO3^-]$$

For achieving electrical neutrality

$$[SID] + [H^+] - [OH^-] - [HCO_3^-] - [CO_3^{-2}] = 0$$

by substituting and clearing, cubic equation like syntax will be produced

$$H^3 + [SID] \times H^2 - (K_C \times P_C + K'_W) \times H - K_3 \text{ x } K_C \text{ x } P_C = 0$$

Curves analysis for presenting H$^+$ behavior:(Figures (14, 15))

- When SID is positive, H$^+$ decreases non-linearly with increasing SID, and increases linearly with PaCO2. For positive SID values, OH$^-$ is always larger than H, the effect of added CO2 is to decrease OH, so the excess strong positive charge measured by SID can be balanced by CO3^{-2} and HCO3$^-$.
- When SID is Negative, with the excess of negative charge strong ion charges, H+ is the only positive weak ions, so under these conditions, OH$^-$, CO3^{-2} and HCO3$^-$ can exist only at very low concentration.

HCO3$^-$ behavior (Figures(16))

Under positive SID condition, HCO3$^-$ is by order of magnitude the largest of the four dependent variables so the rule of electrical neutrality can be written as

$$HCO3^- = SID$$

"SID is equal to HCO3$^-$ numerically , but physically SID determines HCO3$^-$ but not vice verse"

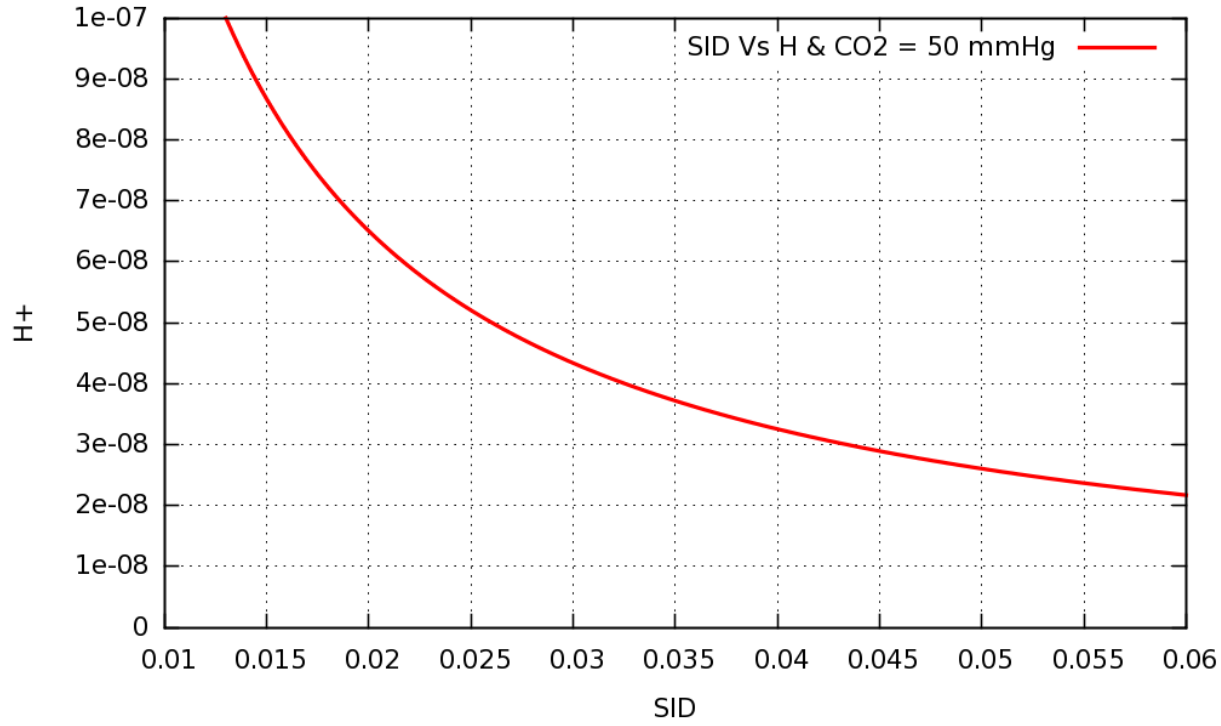

Figure 14: H is plotted against SID "Eq/L" with PaCO2 fixed at 50 mmHg[70]

Another feature from the previous equation$(SID = HCO3^{-})$ is that HCO3 is independent to CO2 *figure(16)*. This conclusion means that if SID is constant and PaCO2 changes, CO3 , OH and H will change but HCO3 will not , therefor *HCO3 is not very useful quantity in the analysis interstitial fluid.*

$CO3^{-2}$ behavior Figures(17 , 18)

From the following curves,CO3 decrease with increasing PaCO2. The most important role of CO3 is probably in Ca homeostasis. The solubility product of CaCO3 is 10e-8 $(Eq/L)^{+2}$, so if $CO3^{-2}$ rise above 10e-5 , Ca^{+2} should fall below 1 mEq/L . In the cases of lowered CO2 such as hyperventilation, that will cause CO3 to rise and thus lowering Ca level which may lead to tetany as classical symptom of hyperventilation.

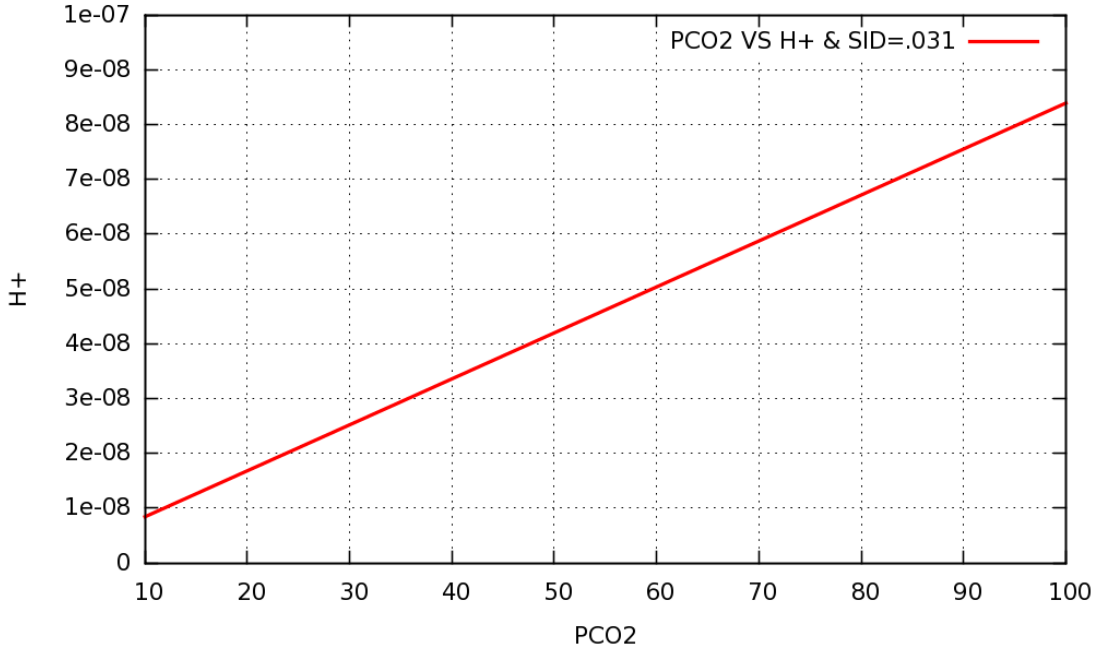

Figure 15: H is plotted against PaCO2 in mmHg with constant SID=0.031 Eq/L[70]

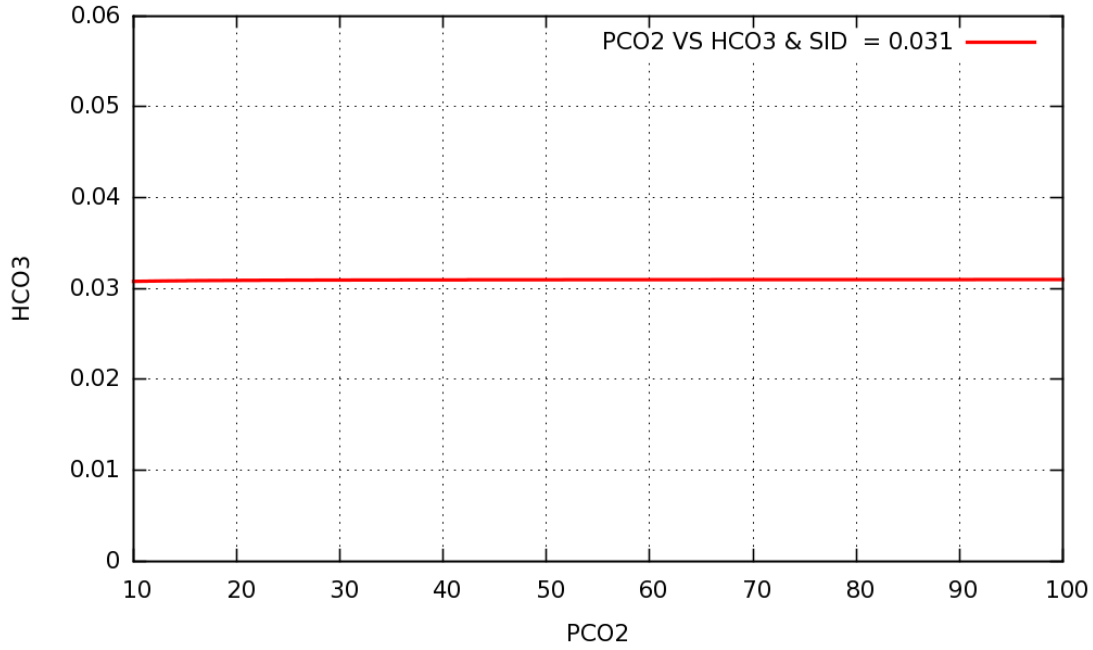

Figure 16: $HCO3^-$ Eq/L is plotted against PaCO2 mmHg with constant SID value at 0.031 Eq/L[70]

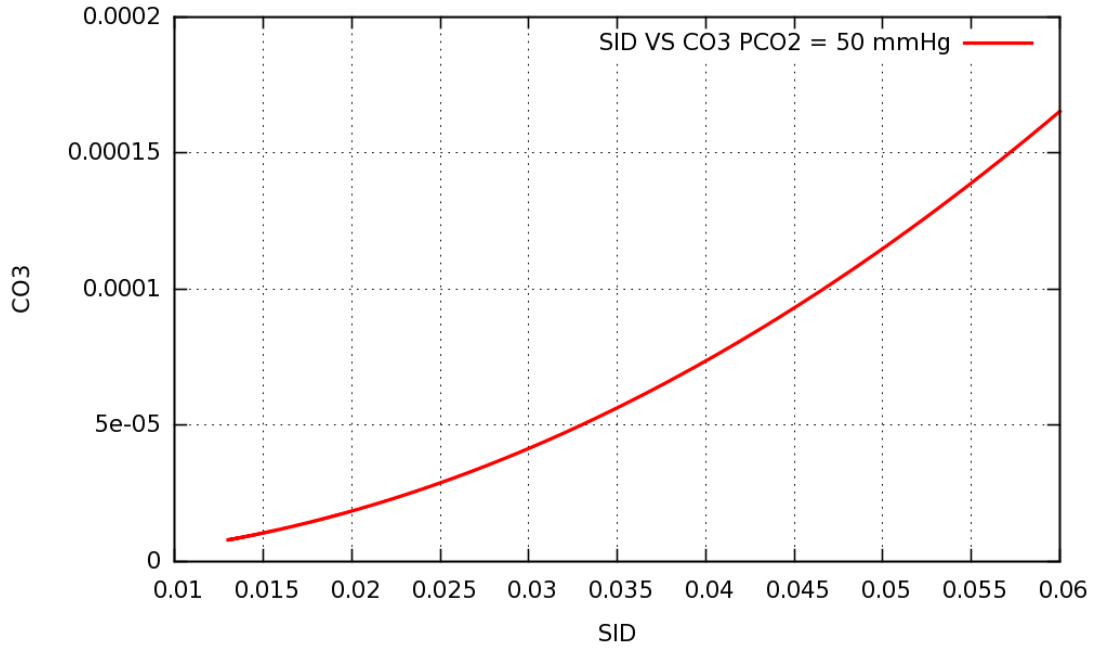

Figure 17: $CO3^{-2}$ is plotted against SID with constant PaCO2 value at 50 mmHg[70]

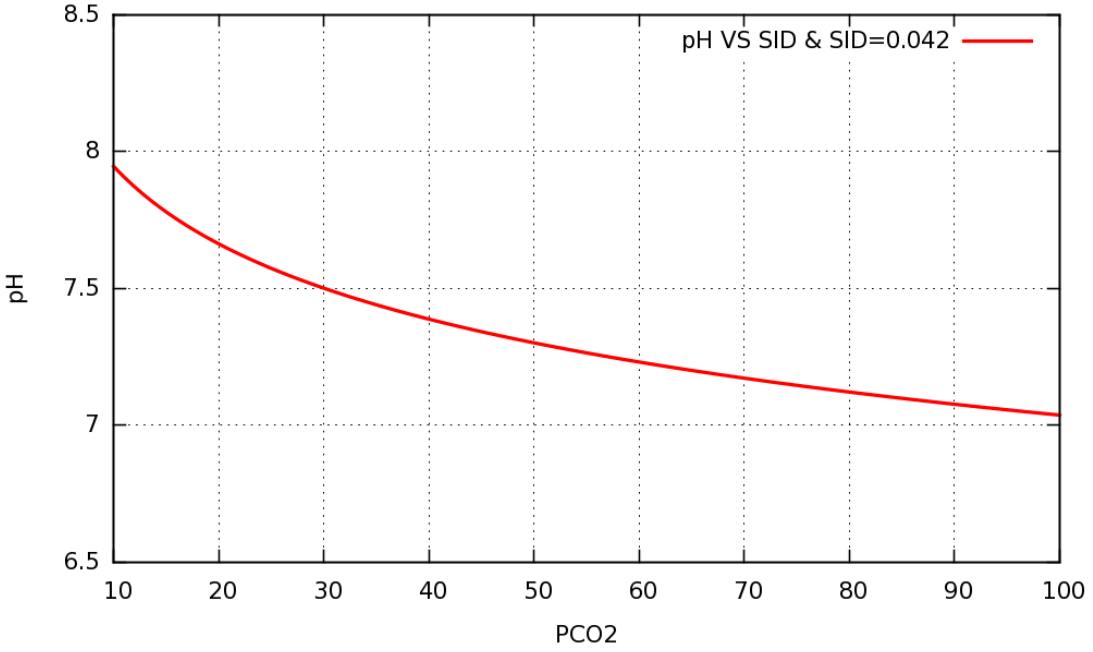

Figure 18: CO3 "Eq/L" is plotted against PaCO2 mmHg with constant SID 0.03 Eq/L[70]

The H^+-CO2 graph Figure 19

After plotting of H^+ and CO2 relationship with known SID, the following information could be concluded

- SID could be evaluated by known H^+ (using pH meter) and known PaCO2, after that, the value of OH^-, $CO3^{-2}$ and $HCO3^-$ could be calculated if needed
- H^+ depends only on SID and PaCO2, adding or removing CO2 or change SID value can only change H^+ value
- H^+ does not depend on $HCO3^-$, $HCO3^-$ was important historically as it could be calculated from known value of CO2 and H^+. although H^+ and $HCO3^-$ values could be calculated from each other but it does not mean that either one physically determines the other.

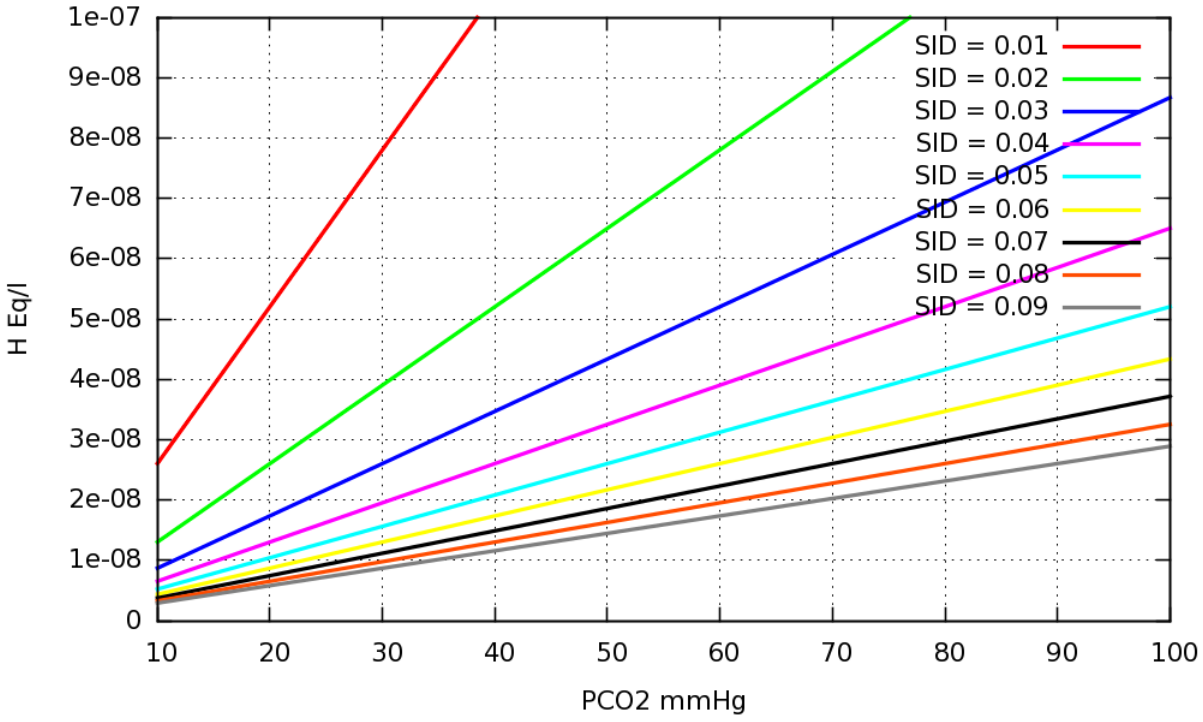

Figure 19: H^+ is plotted against PaCO2 for series of SID values[70]

IV Presentation of relationship between all independent variable , SID , A_{TOT} , and CO_2 and dependent variables

Using the same concepts of low of mass action and rules of electrical neutrality after adding weak acid and applying the electrical neutrality rule the following equation could be concluded[71]:

$$SID + H^+ + HCO_3^- - A^- - CO_3^{-2} - OH^- = 0$$

By substitution for known variables , H^+ value could be expressed in polynomial equation

$$\begin{aligned} H^4 + K_A + SID \times H^3 + K_A \times (SID) - A_{TOT}) - \\ (K_C \times P_C + K'_W) \times H^2 - K_A \times (K_C \times P_C + K'_W + \\ K_3 \times K_C \times P_C \times H - K_A \times K_3 \times K_C \times P_C = 0 \end{aligned}$$

As summary for the relationships between all independent variables

- H^+ and OH^- behavior: H^+ decreases non linearly with increasing positive SID and increases with increasing PaCO2. H^+ is slightly larger in solution at given SID and PaCO2 value than it is in ISF where non weak acid is present *Figures(20)*:
- $HCO3^-$ and $CO3^{-2}$ behavior : $HCO3^-$ in solution increase with increasing positive SID but non linearly. That Could be expressed as

  $$SID = HCO3^- + A^-$$

  $HCO3^-$ in this solution does depend on PaCO2, it increases with increasing PaCO2, although not very rapidly, that is because A^- is also is depending on PaCO2
- A^- and [HA] behavior: With increasing PaCO2, [A^-] falls and HA rise, but not very dramatically. Both quantities are more sensitive to SID change than PaCO2 change.

- The H^+ - PaCO2 behavior : For given SID value, H is larger and more sensitive to PaCO2 in plasma than interstitial fluid.

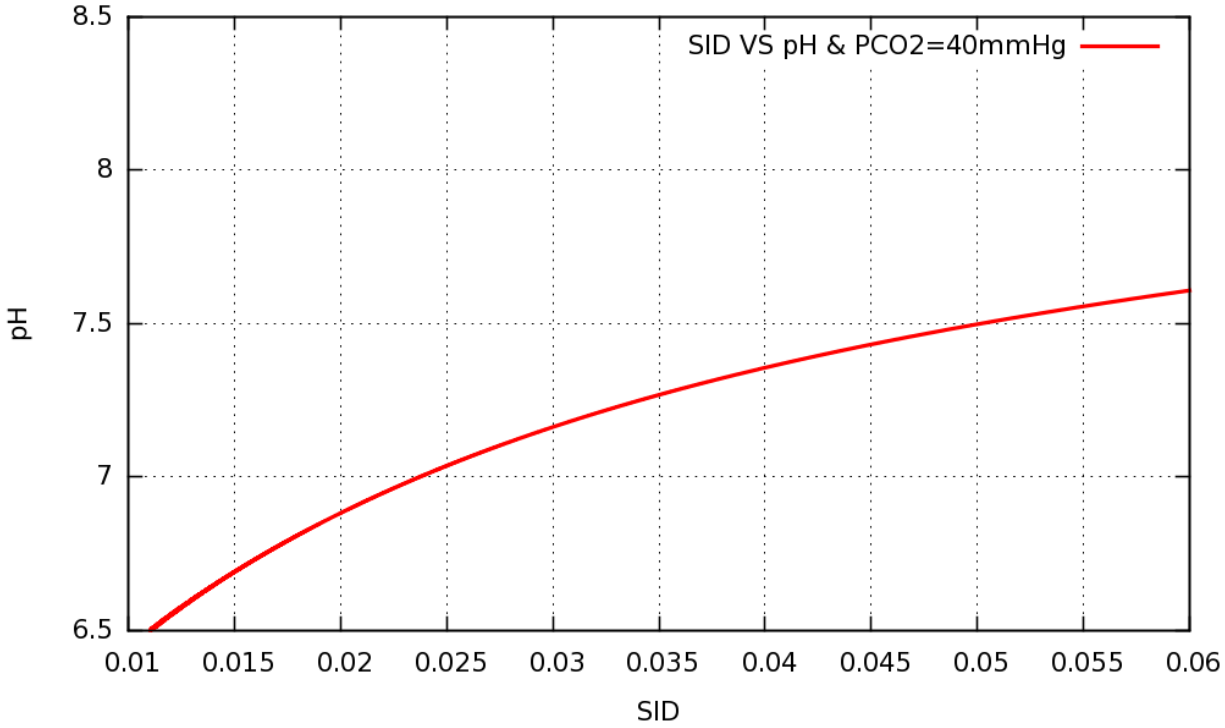

Figure 20: pH plotted against SID with constant CO2 at 40 mmHg[71]

V Whole-body Acid-Base Balance

Acid-base Balance :

is set of mechanisms by which parts of the body, notably lungs, kidneys, and gastrointestinal track, control the composition of circulating blood plasma, so its H^+ lies generally within range from 2×10^{-7} to 1×10^{-7} Eq/L or pH 7.7 to 7.0[72]

Role of lung

Starting by main organ regulator of PaCO2, the lungs. In the lung capillaries, CO2 in circulating plasma equlibrate with CO2 in alveolar gas, the result under

normal conditions is an alveolar and circulating plasma PaCO2 value close to 40 mmHg.

Changing in alveolar ventilation can occur very rapidly "in seconds" and will result in rapid change in arterial plasma PaCO2. The effect on plasma H^+ will be rapid, that could be understood from the *diagram 21* which describes the relationship between H and PaCO2. The area labeled acute are for the patients with short duration PaCO2 abnormality. As expected, increasing PaCO2 will result in elevation of H^+ ion concentration, in acute respiratory acidosis area of relationship lies parallel to lines of constant SID, when PaCO2 falls. There appears to be some change in SID value, the area of acute respiratory alkalosis is not parallel to SID lines. Some of this SID change may be due to strong ion shifts between plasma and RBCs-ICF.In any case, SID effects are small.

Normal breathing frequency is 12 to 20 breaths / minutes, so PaCO2 can change within seconds or minutes. If abnormal PaCO2 value is maintained for hours or days, additional mechanism comes to scene, and that condition is called "*chronic respiratory disorder*", the area corresponding this stat indicate such SID changes more than the acute case, kidney will play role for achieving deviation of SID .

Role of kidneys:

Circulating plasma is perfusing the kidneys at an average rate of about 500 mL/min, almost all filtrate is absorbed and returned to plasma; only about 1mL/min ends up as urine to be eliminated from body.

Strong ions processing by the kidney is important. Every Cl^- filtered but not reabsorbed means corresponding increase in plasma SID, and every Na^+ or K^+ not reabsorbed means a decrease in plasma SID. The kidney volume receptor aldsoterone ECF volume regulating system has net effect of using plasma and ECF, Na^+ as determining variable for plasma ECF volume. The kidney therefore balance net Cl^- execration against net Na execration for regulation of plasma SID.

The acid base balance situation for abnormal PaCO2 concentration can be understood quantitatively as the following: When abnormal PaCO2 is maintained , the kidneys respond by changing SID so as to bring plasma H back toward normal. So the four abnormal areas in *Figure (21)* can be translated to the following terms :

- Acute Respiratory Acidosis = PaCO2 up briefly, so plasma H^+ is up
- Acute Respiratory Alkalosis = PaCO2 down briefly, so plasma H^+ is down
- Chronic Respiratory Acidosis = PaCO2 up "sustained" , SID up ,H^+ up slightly
- Chronic Respiratory Alaklosis = PaCO2 down "sustained", SID down, H^+ down slightly

The conventional description associated change of SID is called in term of compensation, for example "Chronic respiratory acidosis with accompanying metabolic alkalosis".

For Stewart, the term "metabolic" is inappropriate as there are no chemical reaction happened for compensation, the whole game is played here just by ionic charges.

Role of gastrointestinal track :

In the stomach, Cl^- is removed from the plasma circulating through the gastric mucosa and secreting into the lumen as gastric acid. SID in the plasma is increasing, that effect on total circulating plasma is small, but detectable, the classic name for this phenomena is (Alkaline tide).

This series of events are disturbed in cases of prolonged vomiting, transferred Cl^- is lost from body and never returned to plasma. So plasma SID is elevated, and decrease of H^+ "Rise in pH". The patient will be said to have metabolic alkalosis

So alkalosis resulted from loss of Cl^- not loss of H^+ !!

From the H^+ and PaCO2 relationship, plasma H^+ does not fall as much as expected from SID change, that is due to respiratory compensation. PaCO2 rise as SID rise, so respiratory acidosis is superimposed on metabolic alkalosis. Final picture will be

- Lowered plasma CL level "Hypocholermia"
- Elevated SID = Metabolic Alklosis
- Above normal PaCO2 = Respiratory acidosis
- Moderately lowered H = Elevated pH

That have clinical importance of using antacid for treatment of increasing gastric acidity. Ingestion of solid NaHCO3 simply increase SID in the stomach and converts normal negative SID to positive one. Na^+ will be absorbed from small intestine and increase Na^+ load to ECF volume and plasma SID regulating function of the kidney, it should be strictly avoided in patients with heart failure or hypertension.

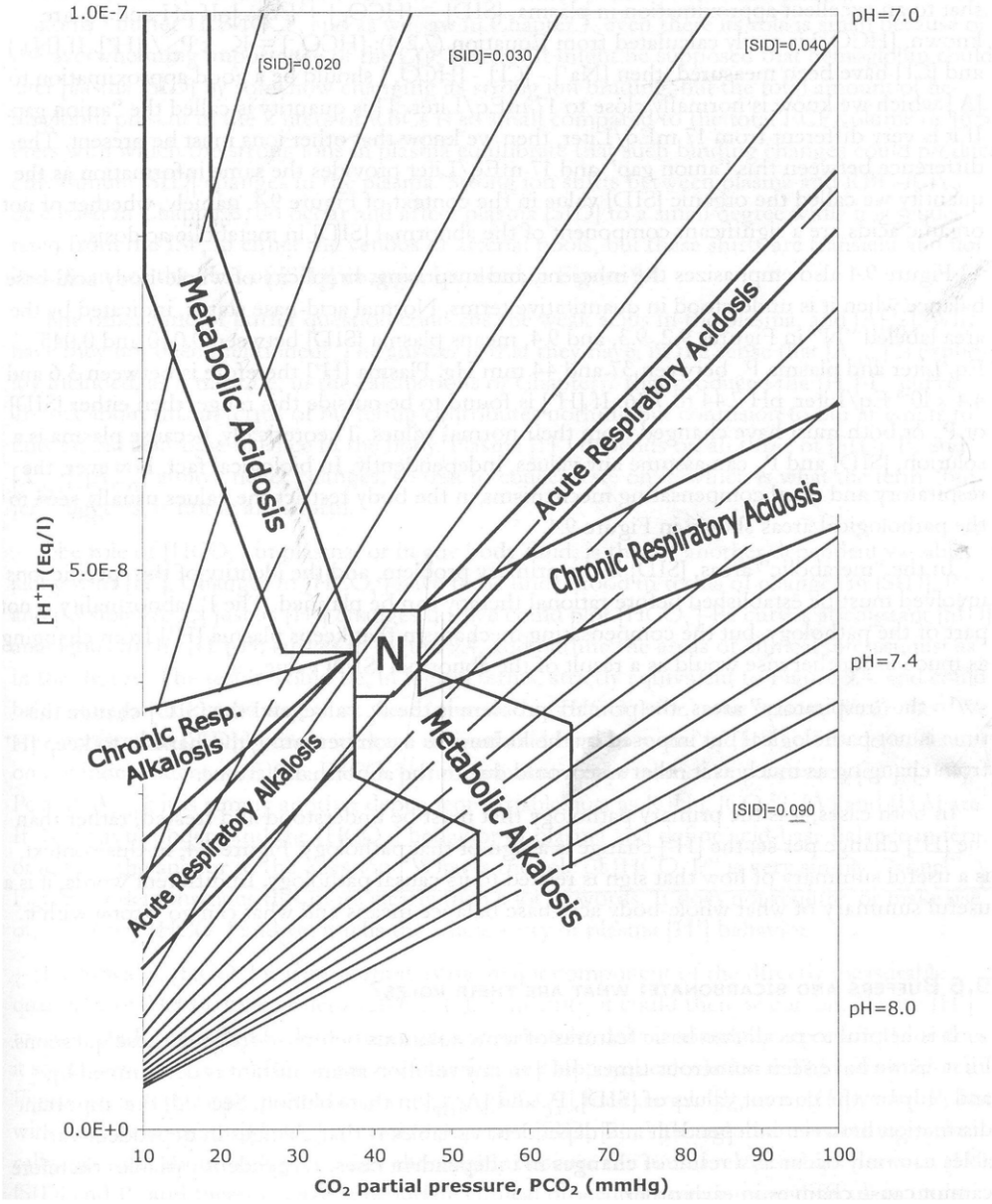

Figure 21: CO2 is plotted against H^+ and pH with different SID values[72]

C Figge-Fencl Modifications

Stewart presented quantitative physicochemical model of human acid base physiology, this model incorporate three fundamental principles

1. The law of conservation of mass is obeyed.
2. Electrical neutrality is maintained.
3. All statements of chemical equilibria are simultaneously satisfied.

Figge and Fencl[73] concentrated in their work on major species of weak acid and their conjugate base. Weak acids which are included in their model are phosphoric acid(phosphate system) , the citric acid (citrate system), and dissociatable amino acid side chain of albumin *Figure (22)*. Plasma globulins plays only minor role in acid base balance, so they are not included in their model.

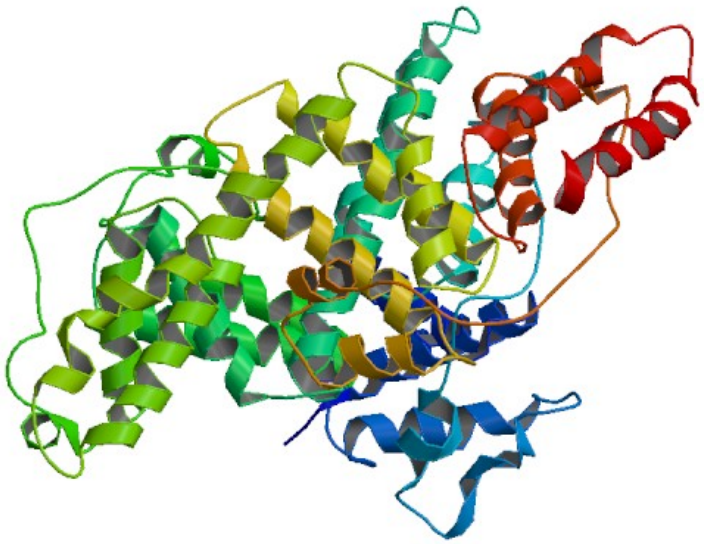

Figure 22: X-ray study of recombinant human serum albumin. phases determined by molecular replacement method[74]

Within the pH range of biological interest (6.8-7.9), the negative charge contributed by albumin in plasma at given pH will be

$$[Z_{Albumin}] = -10 \times [Albumin] \times (0.1204 \times pH - 0.625) :$$

This model can be used using computer applications for illustrating the effect of independent variables on acid base status in plasma like solutions containing albumin[73]

$$pH = f(pH) = SID, PCO_2, [Pi_{TOT}], [Albumin], [Citrate_{TOT}]$$

$$Pi_{TOT} : total\ phosphate, Citrate_{TOT} : total\ citrate$$

Later, Fencl and his colleagues [75] published their comparison between BE approach, bicarbonate concentration with anion gap approach and physicochemical principle. According to physicochemical principle plasma acid base status is determined by independent variable only; PaCO2, [SID], and concentration of non volatile weak acid. Classification of disorders according to that approach[75] *figure(23)* include the following :

1. Respiratory disorder is expressed by deviation of CO2, Increase CO2 will produce acidosis and its decrease will produce alkalosis
2. Non-respiratory component, two types of abnormalities can be accused; abnormal SID and abnormal concentration of weak acid for [SID] the abnormality may be due to water excess/deficit or imbalance
   (a) Regarding to SID, its value can be changes by two ways
      i. Water deficit or excess in plasma e.g "Dilutional Acidosis" and "Concentrational Alkalosis", is detected by abnormal Na concentration
      ii. By changing the total concentration of the strong anions only (this is true because concentrations of strong cations other than Na+ are regulated in extracellular fluids within narrow limits, for purposes unrelated to acid-base balance or osmolarity).
   (b) Regarding to A_{TOT}, two substances present in plasma have concentration great enough to make acid base disturbance

i. Inorganic phosphate ([Pi], millimol per liter or milligrams per deciliter)
ii. Albumin ([Alb], grams per liter)

CLASSIFICATION OF PRIMARY ACID–BASE DISTURBANCES

	Acidosis	Alkalosis
I. Respiratory	↑ P_{CO_2}	↓ P_{CO_2}
II. Nonrespiratory (metabolic)		
1. Abnormal SID		
a. Water excess/deficit*	↓ SID, ↓ [Na^+]	↑ SID, ↑ [Na^+]
b. Imbalance of strong anions		
i. Chloride excess/ deficit†	↓ SID, ↑ [Cl^-]	↑ SID, ↓ [Cl^-]
ii. Unidentified anion excess‡	↓ SID, ↑ [XA^-]	—
2. Nonvolatile weak acids		
a. Serum albumin	↑ [Alb]§	↓ [Alb]
b. Inorganic phosphate	↑ [Pi]	↓ [Pi]‖

Figure 23: Screenshot form Fencl article for classification of primary acid base disturbances[75]

Fencl produced new definition for SID, after application of electrical neutrality concept *figure(24)*, SID can be calculated using the following formula

$$SID = [HCO3^-] + [Alb] + [Pi]$$

The data for evaluation can be gathered from

- Albumin and Pi can be obtained be direct measurement of serum analysis for conversion to mEq/L

$$[Alb] = [Alb] \times (0.123 \times pH - 0.631)$$

$$[Pi] = [Pi] \times (0.309 \times pH - 0.469)$$

- $HCO3^-$ can be available from blood gas measurements so SID can be calculated
- XA^- is the anion other than chloride, it can not be directly measured, its presence indicates disease state. They can be calculated form the following

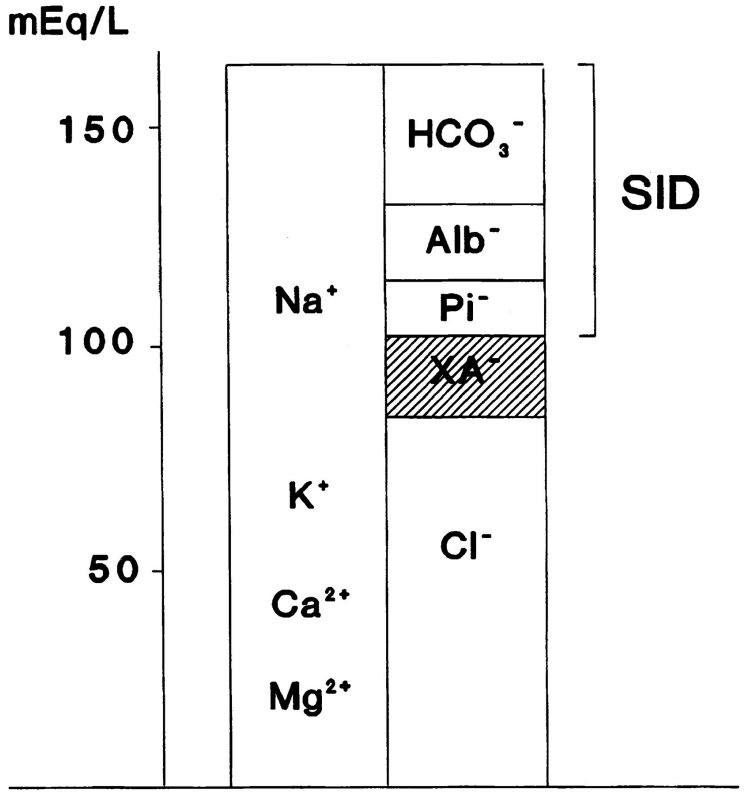

Figure 24: Representation of SID published in Fencl article[75]
Electroneutrality in blood plasma: sum of positive charges equals the sum of negative charges, as indicated by equal heights of the columns representing cations and anions.
Alb and Pi are negative electric charges displayed by serum albumin and inorganic phosphate.
XA$^-$=unidentified strong anions.
SID =Strong Ion Difference.

formula

$$[XA^-] = ([Na^+] + [K^+] + [Ca^{+2}] + [Mg^{+2}]) - [Cl^-] - SID$$

- Water excess and deficit can be detected by Na^+ level but Cl^- level has to be corrected to quantitative its effect after water adding or removal. Corrected chloride can be calculated from the following

$$[Cl^-]_{Corrected} = [Cl^-]_{Observed}([Na^+]_{Normal}/[Na^+]_{Observed})$$

For more simplification Fencl produced the following formula for bed side evaluation of [SID]

$$SID = HCO3^{-} + 0.28 \times Albumin(g/L) + 1.8 \times Pi(mmol/L)$$

D Stewart and Base Excess

Definition:

The quantity of metabolic acidosis or alkalosis defined as the amount of acid or base that must be added to a sample of whole blood in vitro to restore the pH of the sample to 7.40 while the PaCO2 is held at 40 mm Hg. Expressed by the following equation

$$BE = (HCO3^{-} - 24.4 + [2.3 \times Hb + 7.7] \times [pH - 7.4]) \times (1 - 0.023 \times Hb)$$

There is great variability in the equations used for calculating BE. While BE is quite accurate in vitro, inaccuracy has always been a problem when applied in vivo in that BE changes slightly with changes in PaCO2. This effect is understood to be due to equilibration across the entire extracellular fluid space (whole blood plus interstitial fluid). Thus, the BE equation was modified to standardize the effect of hemoglobin on CO2 titration in order to improve the accuracy of the BE in vivo[35]. Expressed by standard base excess equation :

$$SBE = 0.9287 \times (HCO3 - 24.4 + 14.83 \times [pH - 7.4])$$

Wooton[76]developed equation for correction of standard base excess(SBEc) using Stewart quantitative technique by adding the effect of albumin and phosphate expressed by

$$SBEc = [HCO3^{-}] - 24.4 + 8.3 \times Alb \times 0.15 + 0.29 \times Phos \times 0.32 \times (pH - 7.4)$$

Where Alb=Albumin expressed in gram/dl and Phos=Phosphate in mg/dl

In this way [SBEc] can satisfy definition of Base Excess as :
From [SID] definition, it's equal to absolute difference between completely dis-

sociated cations and anions. According to electrical neutrality principle the difference is balanced by weak acid and CO2, according to that concept SID can be defined as "effective strong ion difference" [SIDe] in the term of weak acid and CO2, which identical to "buffer base" term defined by Singer and Hastings[57, 59].

$$SID = [HCO3^{-}] + C_{Alb} \times (8.0 \times pH - 41) + C_{Phos} \times (0.30 \times pH - 0.4)$$

Where C_{Alb} and C_{Phos} are plasma albumin and phosphate concentrations. So, the change of base excess will equal change of SID:

$$\Delta SID = \Delta[HCO3^{-}] + (8.0 \times C_{Alb} + 0.30 \times C_{Phos}) \times \Delta pH$$

SID can be calculated form SIDe]"Effective strong ion difference" : which will equal

$$SIDe = HCO3^{-} + Albumin + Phosphate$$

E Strong Ion Gap "SIG"

Based on Stewart work, Jones[77], introduced new scanning tool. Similer suggestion appeared in Figge work 1992, Kellum and colleague called it "The Strong Ion Gap"[78, 79, 80].
The Concept is based on that there are two ways for measuring SID, the difference between them is called "Strong ion Gap" [SIG] .
"Apparent Strong Ion Difference" SIDa : which will equal

$$SIDa = Na^{+} + K^{+} + Ca^{+2} + Mg^{+2} - Cl^{-} - Lactate^{-}$$

And SIDe "Effective strong ion difference ": which will equal

$$SIDe = HCO3^{-} + Albumin + Phosphate$$

Which presents weak ionic inverse of SID, calculated as total plasma concentration of weak negative ions A^{-}+$HCO^{-}3$, where A^{-} is ionized component of albumin and phosphate, so

$$SIG = SIDa - SIDe$$

$$SIG = [Na^{+}] + [K^{+}] + [Ca^{+2}] + [Mg^{+2}] - [Cl^{-}] - [Lactate^{-}]$$
$$-[Alb] \times (0.123 \times pH - 0.631)$$
$$-[PI] \times (0.309 \times pH - 0.469$$
$$-0.0301 \times PaCO2 \times 10^{(pH-6.1)}$$

SIG is used to predict the presence of unmeasured ions Normal values *figure(25)*, According to kellum it should equal zero in normal subject but it was found it may varies between 5-8 mEq/L in critically ill patients [81]

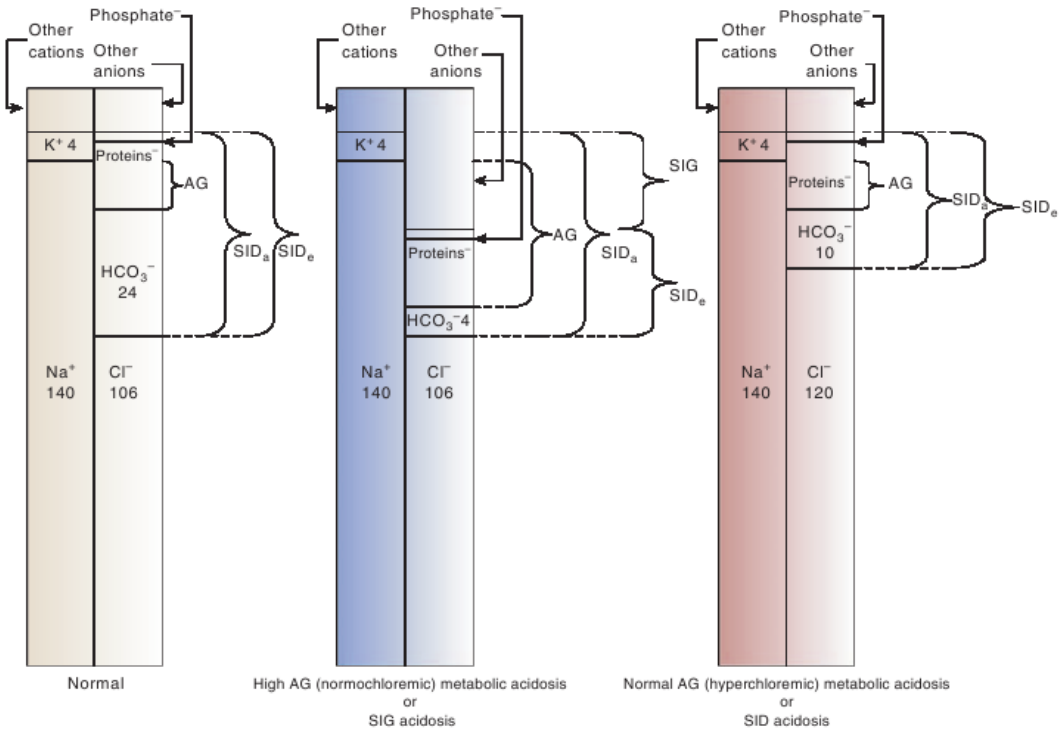

Figure 25: Schematic illustration of plasma cations and anions [82]
in normal acidbase status, high-anion-gap (normochloremic)metabolic acidosis or SIG acidosis, and normal anion gap (hyperchloremic) metabolic acidosis or SID acidosis. The numbers within the bars give ion concentrations in millimoles per liter. AG, anion gap; SID, strong ion difference; SIDa, apparent strong ion difference;SIDe, effective strong ion difference; SIG, strong ion gap

F Simplification of Stewart-Fencl approach

Balasubramanyan and colleagues [83] have used the Stewart concept and base excess approach for examination of effect of Base Excess on two independent variables "SID and total weak acid concentration". They called their approach "Base excess to Stewart Fencl approach".

Gilfix [84] and colleagues, used the work of Figge and colleagues [73] to drive four equations for estimation of the effect of base excess on SID and weak acid concentration, they used Na^+ And Cl^- as the main strong ions in plasma and albumin as main weak acid.
Story and his colleagues[85], in their research simplify the four equations to more simple formula that can be calculated mentally.Fencl divided the effect of SID on base excess into Na^+ and Cl^- effect expressed by the following equations:

$$Na^+ \text{ effect on BE } = 0.3 \times ([Na^+] - 140)\ mEq/L$$

$$Cl^- \text{ effect on BE } = 102 - ([Cl^-] \times 140/[Na^+])mEql/L$$

Now SID effect Na effect minus Cl effect will equal

$$\text{SID effect} = 0.3 \times ([Na^+] - 140) + 102 - ([Cl^-] \times 140/[Na+])$$

The median value for sodium is 140 mEq/L and that for chloride is 102 mEq/L . Therefore the median difference is 38 mEq/L So, SID effect

$$\text{Sodium-Chloride effect(mEq/litre)} = [Na^+] - [Cl^-] - 38$$

as albumin is main representative to plasma weak acid concentration , as Figge and colleagues developed a pH-dependent formula for the anionic effect of albumin

$$\text{Albumin anionic effect (mEq/litre)} = (0.123 \times pH - 0.631) \times Albumin(g/litre)$$

So, change of albumin concentration will change of its anionic effect which will change its effect on BE For more simplification the equation is simplified into

"using single pH of 7.4"

$$\text{Albumin effect (mEq/litre)} = 0.28 \times [42 - Albumin(g/litre)]$$

For facilitation of mathematical calculation

$$\text{Albumin effect (mEq/litre)} = 0.25 \times [42 - Albumin(g/litre)]$$

So, four equations can be summarized as the following,

Standard base excess (mmol/litre=meq/litre) from a blood gas machine

$$Sodium\text{-}chloride\ effect\ (meq/litre) = [Na+] - [Cl-] - 38$$

$$Albumin\ effect\ (meq/litre) = 0.25 \times [42 - albumin(g/litre)]$$

Unmeasured ion effect (mEq/litre)=
Standard base excess-(sodium-Chloride effect)-albumin effect.

As example for their alternative approach, Story and his colleagues presented example for case doing gynecological procedure *table(3)*. Two sample were drown, first sample just after induction of anesthesia , the other after 2 hours of surgery. Normal saline was used as intraoperative fluid

Table 3: Acid Base Changes after induction and after 2 hours[85]

	After induction	After 2 hours
pH	7.41	7.28
Carbon dioxide (kPa)	5.3	5.3
Sodium (meq /litre)	140	142
Chloride (meq/ litre)	104	115
Albumin (g/ litre)	40	28
Base excess (meq/ litre)	-0.4	-6.7
Sodiumchloride effect (meq/ litre)	-2	-11
Albumin effect (meq/ litre)	0.5	3.5
Unmeasured ion effect (meq/ litre)	1.1	0.8

"In this patient, after 2 h of surgery most of the metabolic acidosis can be explained by a decrease in the strong ion difference secondary to an increase

in plasma chloride. This is partly offset by a decrease in the total weak acid concentration (albumin). Unmeasured ions are unimportant in this acidaemia. These changes follow the infusion of about 6 litres of 0.9% sodium ".

G Buffering and buffers "SID generators"

In his book, Stewart established the buffering definition using SID and ATOT as independent variables and dependent variables *Figure(12)*. In solutions containing strong ions only, Hydrogen ion is determined only by SID. In solution contains strong ions and weak acid, the value of H^+ is determined by two independent variables "SID" and "ATOT" . If SID ranges from zero to "ATOT", change of hydrogen ion will be less than in situation of absence of "ATOT".

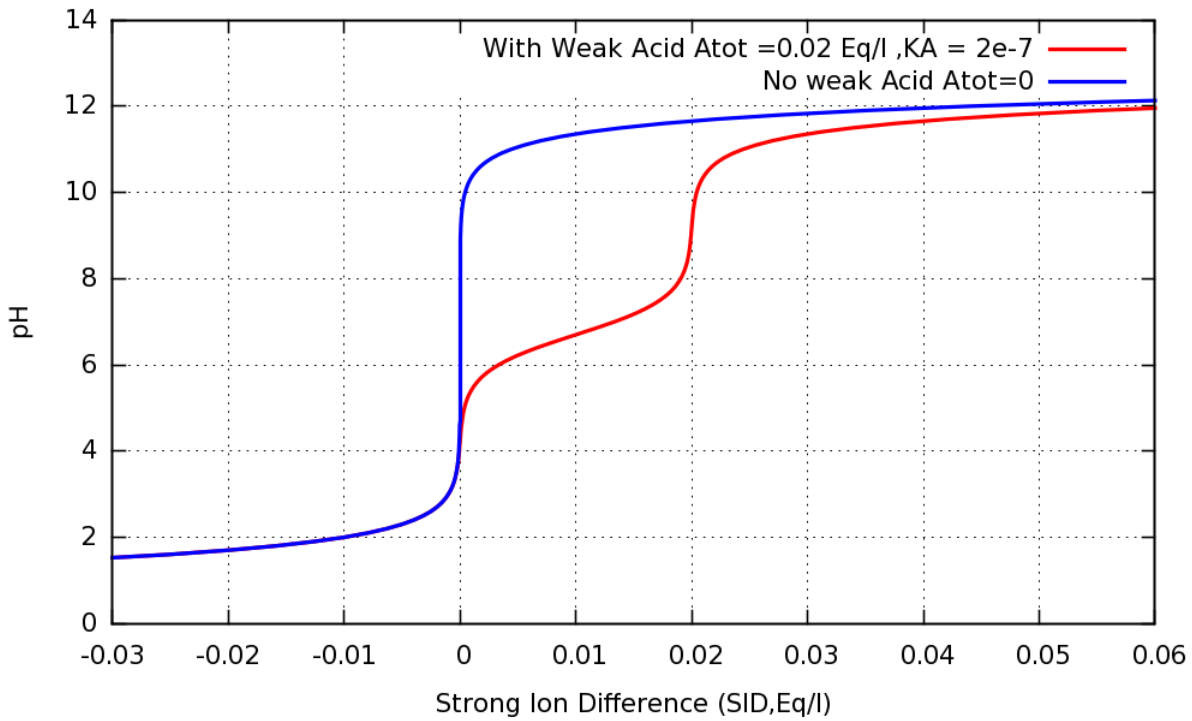

Figure 12: pH is plotted against SID in the presence and absence of [ATOT]

The presence of weak acid does make important difference, it changes the H^+ of solution at any SID value to more acidic condition, the weak acid change

the point around which H^+ changes,for given range of SID value. It does not decrease the amount of H changes; in fact it increases it. So weak acid "buffer is not pH regulator bu it's pH setter" .

Quantitatively, the ability of solution to resist the change in H^+ in response to SID is determined by slope of H^+ or pH versus SID curve, steeper of curve the greater H^+ or pH changes.
For positive SID values of solution contains strong ions only

$$H^+ \text{ buffer strength } = \frac{[SID]^2}{K'_W}$$

So

$$\text{pH buffer strength } = 2.3 \times [SID] Eq/L$$

For example two solutions with the following information: *No weak acid solution*" with SID = 0.01 and "*weak acid solution*" with same SID and Ka = 2.0e-7 Eq/L , by application of the previous equations: From the previous

Solution	H buffer strength	pH buffer strength
No weak acid	-2.3×109	0.02 Eq/L
Weak Acid	-2.5×104	0.01 Eq/L

curve, the corresponding change of H^+ is much larger in weak acid containing solution than SID containing one. Stewart along his book chapters explain buffer strength of each individual independent variables and put it in quantitative footing.

For clinical gain form different concept of buffering, by analyzing of alkalizing agents we will get different view of "What is really happening if??"

1. **Giving bicarbonates**
   The relationship between arterial PaCO2 and pH can be demonstrated by the following *figure(26)*

   The normal curve position "at BE [0]" that is normal pH at given value of CO2. Shifting the cure upward "at BE +10 and +20" means associated primary metabolic alkalosis or compensation for respiratory acidosis,

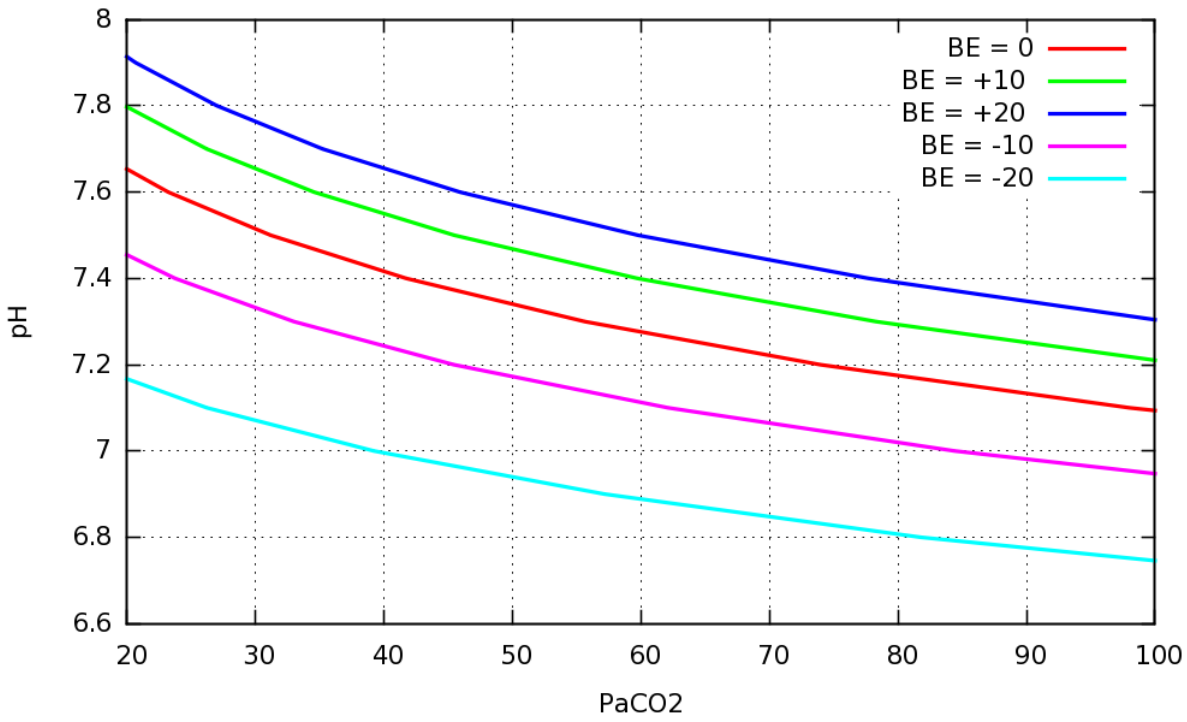

Figure 26: PaCO2 is plotted against pH with different value of Base-excess [69]

shifting of the curve downwards "at BE -10 and -20" means that might be either primary metabolic acidosis or as compensatory consequence. The administration of sodium bicarbonate causes shift of the curve upward, so the corresponding pH will be higher than it was previously relative to PaCO2.

According to Stewart concept, the bicarbonate here have nothing to do to H^+ or pH, Since NaHCO3 has no $A_{[TOT]}$ activity, Na^+ as strong anion which will play the major role.

By application of the previous consideration, shifting of the curve upward will result in increasing SID or decreasing ATOT or both and reverse is right considering downward shift of BE curve.

Adding NaHCO3 will cause :

(a) Increasing [SID], SID of 1 M NaHCO3 solution is 1000 mEq/L, which is twenty five times that of extracellular fluid

(b) Due to volume adding and shifting of fluid from intracellular to ex-

tracellular space due to hypertonicity, some collateral $A_{[TOT]}$ dilution event will happen but it plays a minor role

The unimportance of $HCO3^-$ can be demonstrated by receiving same dose of sodium hydroxide, away from side effects, the same upward shift happenes.

Paradoxical intracellular acidosis

Carbonation of NaHCO3 has a downside, since a large amount of CO2 is introduced compared to other combinations like CO2 balanced solution or atmospheric equilibration fluid , so even very small CO2 partial pressure, considerable amount of CO2 will be generated.

Classically, it was thought that sudden intravascular bolus of CO2 will equilibrate across cell membranes, according to that theory this hypercarbic surge may be enough to cause brief but widespread reduction in intracellular pH, this will be undesirable for myocardium of shocked patient .

These considerations are right in vitro situation. But in vivo dealing with hermetically sealed space it's different. Dealing here will be with several communicating compartments and system far from being closed. CO2 can diffuse away rapidly to a much larger volume, so any intravasculer generated CO2 will equilibrate with interstitial and intracellular spaces, then escaping into atmosphere through blood-air interface in the lung.

Hypercarbic surge will be maximal adjacent to cannula where large amount of NaHCO3 solution will mix with small amount of blood, by the time while reaching right atrium considerable dilution happens. Even infusion through central line, the amount infused will be diluted by the high caval flow, reducing the severity of any sudden surge. after that CO2 will exit the body through pulmonary capillaries to lungs, so lung capillaries act as "Safety Valve", so tissue CO2 will be determined by integration of local CO2 production and regional blood flow, so bicarbonate induced Hypercarbia appears to be mild and overestimated. Researchers found that it was

necessary to infuse 1.5 mmole/kg of sodium bicarbonate over 5 minutes, just to generate a detectable PaCO2 and "*CO2 elimination rate*" VCO2 response .

The real PaCO2 can be demonstrated by modeling the extracellular fluid as 20 L fluid compartment with mean hemoglobin concentration 50 g/L "Basic model of standard base excess". If we started with -15 mEq/L, we need to add 300 mmol of sodium bicarbonate to resolve metabolic acidosis. That is a large dose incorporating 6.71 of CO2 ,however to establish normocapnia only 1.41 require subsequent elimination (no compensatory hypocapnia is required once acidosis is corrected).

If the normal VCO2 is 180 mL/min , after infusion of 300 ml bolus over one hour , the extra CO2 burden will be 23 ml /min only[86, 87]

To summarize,

(a) CO2 burden is far less than total volume of infused CO2

(b) The right heart and pulmonary vasculature are the most vulnerable to transient hypercapnia

(c) Other organs are subjected to mild arterial hypercapnia , only when large doses of NaHCO3 are administrated rapidly

(d) For clinical practicing, administration of NaHCO3 should be slowly over 30-60minutes , to spread CO2 burden and reduce VO2 peak .The exception are during cardiac arrest and extreme reduction in pulmonary circulation

(e) Slow administration does not prevent other side effect of sodium bicarbonate such as increase hemoglobin-oxygen affinity , production of hyperosmolar state , reduced Ca^{++} and Mg^{++} and appearance of rebound metabolic alkalosis when organic acidosis resolved

2. **THAM**:
Adding weak base shifts that PaCO2/pH curve upward. THAM, known as tromethamine or "tri buffer" , it has pK_a of 7.7 at 37 $^\circ$ C. Infusion

of THAM will produce new independent acid base variable, "total base" B_{TOT} where

$$B_{TOT} = [THAM - NH_2] + [THAM - NH_3]$$

At physiological pH over half of administrated THAM circulate as THAM-NH_3, by this means THAM change electrical neutrality equation. There is an immediate counter increase in the concentration of buffer base anions (A^- + $HCO3^-$), in the other word, THAM will increase standard base excess without change of SID or $A_{[TOT]}$[88]

Problems associated with THAM infusion[88]:

(a) THAM is CO2 consuming. Intravenous administration reduces VCO2 transiently, in addition with prolonged metabolic alkalosis, that may cause sudden apnea.

(b) THAM is eliminated by the kidney, and will accumulate in renal failure. Other reported problems include hyperosmolarity, coagulation disturbance and hypoglycemia.

H Intraoperative Fluid Management

Administration of fluids exert their acid-base effect via manipulating the independent variables (SID, A_{TOT}, and PaCO2). This become more important if large amount of fluids are administrated in prolonged operations for compensation for blood, evaporation loss, and anesthesia induced vasodilatation [89].

Scheingraber and colleagues[90] showed that infusion of 0.9% saline with rate 35ml/kg/hour will produce metabolic acidosis related to SID change in origin

"The main finding of this study was a rather impressive acidosis (7.41 to 7.28) after a relatively brief interval (2 h) of 0.9% saline infusion, but not after lactated Ringer's solution infusion at rates of approximately 35 ml /kg/h during anesthesia and surgery. This acidosis with the 0.9% saline

infusion clearly had a metabolic origin, because PaCO2 was kept constant and there was no lactic acidosis, because lactate even decreased slightly"

Later, using Stewart method, other studies were published showing the acid-base changes related to TURP operations[91], heamodilution associated with albumin or HES, and infusion of 20% albumin[92]

"The infusion of a total of 1 g/kg body weight of a 20% albumin solution elicited a mild acidification, irrespective of the underlying acid-base status of the patient brought on by prior infusion of either saline or lactated Ringers solution"

1. **Infusion of Crystalloids:**
   Crystalloids administrated during anesthetic practice don't contain weak acid, this means it will decrease plasma [A_{TOT}] which may decrease plasma H^+ (metabolic alkalosis), but since these fluids have SID equals zero, the plasma SID will decrease which will cause decrease in H^+ value (metabolic acidosis). The optimum fluid used in resuscitation is that which its SID is about 24. Its alkalanizing effect of decrease in [A_{TOT}] which is offset by acidifying effect of decrease SID. Similarly, fluid with SID $>$ 24 mEq/L will decrease H^+ while fluid with SID $<$ 24 mEq/L will increase H^+[93]

2. **Colloid Administration**
   Starch based colloids have SID = Zero they will have acidifying effect. Albumin (SID=30 mEq/L) and gelatin preparations (SID = 50mEq/l). In addition they contain A_{TOT} which means the alkalizing effect of ATOT decrease will be less pronounced[94]

3. **Blood loss and blood transfusion**
   Intraoperative blood loss will cause decrease of SID due to lactic acidosis. The preservative solutions of blood or packed RBCs contain sodium citrate. Citrate is a strong anion which is rapidly metabolized in liver which cause SID to become positive, causing alkalosis. However this scenario is not applicable in hepatic impairment patients[95].

I Toward a unified theory of acid-base behavior

On Chmical ground Corey[4] explained "Ion Equilibrium theory" for trail to unify Stewart approach with carbonate buffer system using Henderson Haselblach equation , and non carbonate buffer using Van Slyke.

"Based upon standard thermodynamic equilibrium equations, the ion equilibrium theory links together the various models of acid-base behavior. One enumerates "proton binding sites" to derive the "traditional" model while one enumerates ion charge to derive the Stewart model."

Guenther[96], an analytic chemist, has suggested a "master equation" for solving complex acid-base problems, the following formula was concluded for unification

$$\Delta CB = \Delta SID = \Delta VSSB = \Delta BE$$

CB, the total concentration of proton acceptor sites in solution.VSSB, Van Slyke defined standard bicarbonate.

the previous formula indicates that for normal plasma, changes in total titratable base, strong ion difference, Van Slyke standard bicarbonate, and base excess are all mathematically equivalent. On practical ground all methods can be used together for quantitative and more accurate analysis for acid base disturbances, traditional approach can be used for giving general idea about total acid base disturbances, Stewart approach can be used for further analysis of metabolic element for viewing different element participation in disturbance, for example, determines the rule of albumin in changing of pH, more detailed analysis for effect of volume status on acid base balance and differentiation between types of acidosis "hypercholermic acidosis" and "Unknown anion acidosis"[97].

Chapter 5

Structured approach to assessment Using Stewart-Fencl approach

1. Check history for detecting expected acid base deviation
2. The following data are required for interpretation

$$Na^+, Cl^-, K^+, Albumin, PCO_2$$

3. Calculate corrected chloride "Corrected Cl" for assessment of volume status incorporation in acid base status

$$Corrected\, Cl^- = Observed\, Cl^- \times (Normal\ Na^+ / Observed\, Na^+)$$

4. Calculate apparent SID "SIDa"

$$SIDa = (Na^+ + K^+ + 6) - Cl^-$$

(6) = value for presentation of Ca^{+2} and Mg^{+2} value "provided they are normal"

5. Calculated effective SID "SIDe"

$$SIDe = HCO3^- + 2.8 \times Albumin\ in\ g/dL + 2$$

(2) in SIDe equation for substitution of phosphorus [Pi] value as it not routinely measured

6. HCO3 usually measured by arterial blood gas machine or it could be calculated using Hasselbalch equation
7. Calculate strong ion gap (SIG) or effect exerted by unknown anions "XA^-"

$$SIG = XA^- \ effect \ = SIDa - SIDe$$

8. Make comparison for calculated data to its reference range

Normal Na	138-142 mEq/l
Normal Corrected Chloride	100-108 mEq/l
Normal PaCO2	35- 44 mmHg
Normal albumin	38-45 g/L
Normal SIDa	40-46 mEq/l
Normal SIDe	36-40 mEq/l
XA effect	2-8 mEq/L

9. the whole acid base deviation due to independent variable effect may be observed by calculation of Corrected SBE
10. The possibilities of acid-base disturbance
    (a) Respiratory acidosis due to elevation of PaCO2 above 45 mmHg.
    (b) Respiratory Alkalosis due to decrease of PaCO2 below 35 mmHg
    (c) Hypercholermic acidiosis due to elevated corrected chloride above 108 mEql/L
    (d) Hypocholermic alkalosis due to reduction of corrected chloride below 100 mEq/L
    (e) Hypoalbuminemic alkalosis due to decrease of albumin value
    (f) hyperalbuminemic acidosis due to increase of albumin value
    (g) XA^- "unknown anion" acidosis due to presence of anions that are not routinely measured "as ketone bodies, lactate,..."

A Application of Stewart approach Using Computing method

acidbase.org is providing analysis module interpretation of complex acid base disorder.The program receives data either by regular webform or using URL string for entering data *figures (27,28)*. Site also provides search engine for searching the previous data entry.
In its help files, method of interpretations and mathematical model were presented in easy way connected to input data and result.

[AcidBase.org]

[Home] · [Read the Book] · [Analysis Module] · [Links] · [In Memory of Peter Stewart]

[Analysis Module start] · [Search the Database] · [Warning] · [Glossary] · [downloads] · [write to us] · · · · [intensive care and emergency medicine ultrasound]

normal and abnormal value ranges and their interpretations as used on the acidbase.org website

value to be calculated	units	very low values	moderately low values	slightly low values	therapeutic or normal range	slightly high values	moderately high values	very high values
pH		< 7.1 severe acidosis	7.1 <==> 7.25 moderate acidosis	7.25 <==> 7.35 slight acidosis	7.35 -- 7.45	7.45 <==> 7.5 slight alkalosis	7.5 <==> 7.6 moderate alkalosis	> 7.6 severe alkalosis
lactate	mmol/l				up to 2.2	2.2 <==> 3 slight lactic acid metabolic acidosis	3 <==> 7 moderate lactic acid metabolic acidosis	> 7 severe lactic acid metabolic acidosis
albumin the most prominent of the weak acids read more!	g/l	< 15 severe hypalbuminaemia - metabolic alkalosis	15 <==> 28 moderate hypalbuminaemia - metabolic alkalosis	28 <==> 38 slight hypalbuminaemia - minimal metabolic alkalosis	38 -- 45	45 <==> 60 slight hyperalbuminaemia - metabolic acidosis	60 <==> 70 moderate hyperalbuminaemia - metabolic acidosis	> 70 severe hyperalbuminaemia - metabolic acidosis
PCO2	kPa	< 2.5 severe respiratory	2.5 <==> 3.5 moderate respiratory	3.5 <==> 4.7 slight respiratory alkalosis	4.7 -- 5.9	5.9 <==> 7 slight respiratory acidosis	7 <==> 8.9 moderate respiratory	> 8.9 severe respiratory acidosis

Figure 27: Acidbase.org analysis module "Normal and abnormal value ranges and their interpretations as used in interpretation"

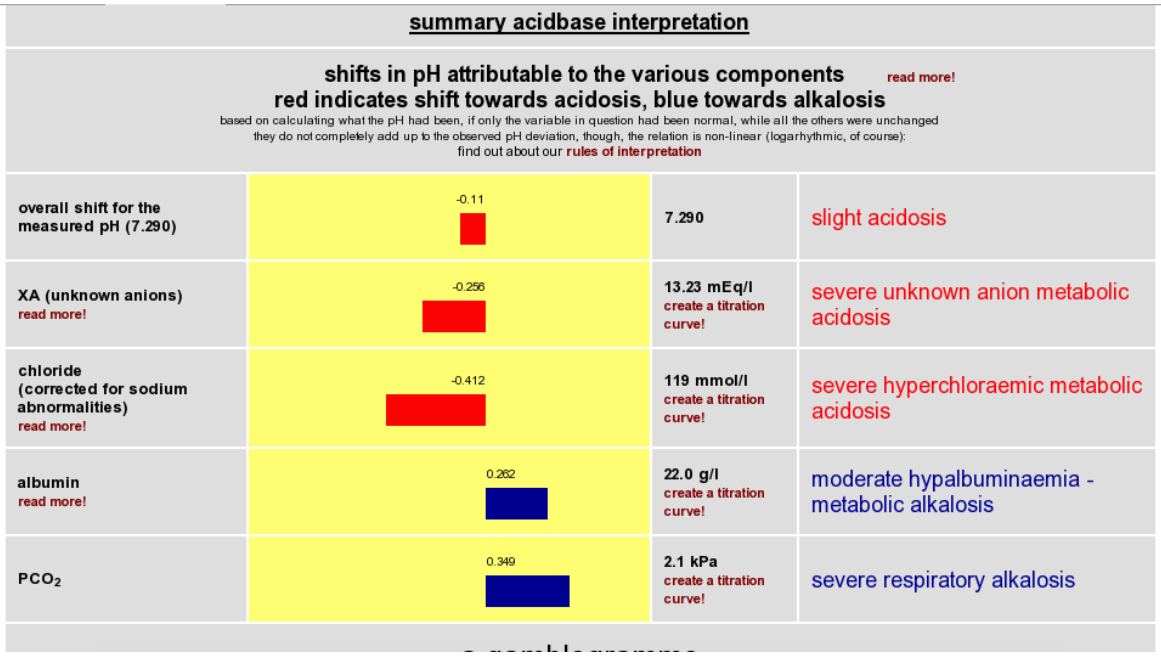

Figure 28: acidbase.org analysis module "Methyl alcohol poisoning case" shift of pH to various component

Summary

Management of acidbase disorders begins with accurate diagnosis, a process requiring two tasks: First, reliable measurement of acidbase variables in the blood. Second, proper interpretation of the data in relation to human health and disease allowing definition of the patients acidbase status.

In this essay we have assessed 3 approaches for interpretation of acid base disturbance, physiological approach which based on Henderson Hasselbalch equation , Base excess approach , based on work done by Ole Sigaard-Andersen, and physiochemical approach based on work done by Peter Stewart.

physiological approach considers acid as hydrogen ion donor and base as hydrogen ion acceptor. pH is determined by level of carbonic acid "PaCO2, controlled by respiratory system " and bicarbonate concentration as metabolic component. The physiological approach determined four situations of disturbance of acid base status

1. Respiratory acidosis "due to increase of PaCO2"
2. Respiratory alkalosis "due to decrease of PaCO2"
3. Metabolic acidosis "presented by decrease in $HCO3^-$ concentration"
4. Metabolic alkalosis "presented by increase in $HCO3^-$ concentration"

Secondary response to the primary disorder is produced to minimize its effect on pH, this secondary response called "Compensatory", absence of secondary response indicates presence of another co-existing acid base disorder "Mixed Disorder".

Blood Base excess was introduced for replacement of $HCO3^{-}$ as metabolic component that is independent from respiratory component. Base excess represents the amount of acid or alkali that must be added to 1 l of blood exposed in vitro to a PaCO2 of 40 mm Hg to achieve the average normal pH of 7.40. Acid is required when blood pH is higher than 7.40 (positive BE or base excess), whereas alkali is needed when blood pH is lower than 7.40 (negative BE or base decit). Normally BE value around Zero .

BE approach recognize 4 acid base disturbances

1. Metabolic acidosis "presented by Base Deficit"
2. Metabolic alkalosis "presented by Base excess"
3. Respiratory acidosis "elevation of PaCO2"
4. Respiratory alkalosis "reduction of PaCO2"

Stewart approach considered pH and H is dependent variables which are dependent on independent variables. Any change in H^{+} or pH value will be controlled by one of the following:

1. Strong ion difference [SID], it is the difference between strong anion and cations
2. Total Acid [A_{TOT}] mostly presented by albumin and inorganic phosphate
3. PaCO2 as respiratory component representative.

By application of approach we get six states of disorder:

1. Acidosis with normal Strong ion gap [SIG]
2. Acidosis with High Strong ion gap [SIG]
3. Hypoalbuminemic alkalosis
4. Hyperalbuminemic acidosis
5. Respiratory Acidosis related to increase in PaCO2
6. Respiratory alkalosis related to decrease in PaCO2

In practical field, it is more easy and usual to use traditional methods for emergency diagnosis of acid base disorder, however in ICU it's better to use quantitative approach for detecting hidden or additional disorders

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