

# History of Medical Understanding and Misunderstanding of Acid Base Balance

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## ABSTRACT

To establish how controversies in understanding acid base balance arose, the literature on acid base balance was reviewed from 1909, when Henderson described how the neutral reaction of blood is determined by carbonic and organic acids being in equilibrium with an excess of mineral bases over mineral acids. From 1914 to 1930, Van Slyke and others established our acid base principles. They recognised that carbonic acid converts into bicarbonate all non-volatile mineral bases not bound by mineral acids and determined therefore that bicarbonate represents the alkaline reserve of the body and should be a physiological constant. They showed that standard bicarbonate is a good measure of acidosis caused by increased production or decreased elimination of organic acids. However, they recognised that bicarbonate improved low plasma bicarbonate but not high urine acid excretion in diabetic ketoacidosis, and that increasing  $p\text{CO}_2$  caused chloride to shift into cells raising plasma titratable alkali. Both indicate that minerals influence pH. In 1945 Darrow showed that hyperchloraemic metabolic acidosis in preterm infants fed milk with 5.7 mmol of chloride and 2.0 mmol of sodium per 100 kcal was caused by retention of chloride in excess of sodium. Similar findings were made but not recognised in later studies of metabolic acidosis in preterm infants. Shohl in 1921 and Kildeberg in 1978 presented the theory that carbonic and organic acids are neutralised by mineral base, where mineral base is the excess of mineral cations over anions and organic acid is the difference between mineral base, bicarbonate and protein anion. The degree of metabolic acidosis measured as base excess is determined by deviation in both mineral base and organic acid from normal.

**Key words:** History, Acid base, Oxygen, Carbon dioxide

## HISTORY

In 1909 Lawrence Henderson at Harvard described how the neutral reaction of blood is determined by carbonic and organic acids being in equilibrium with an excess of mineral bases over mineral acids [1]. He set down his now familiar mass action equation stating that the hydrogen ion concentration is proportional to the ratio of carbonic acid to bicarbonate, placing bicarbonate at the centre of the acid base stage.

Between 1914 and 1930, Donald Van Slyke and others at the Rockefeller Institute elegantly established our acid base fundamentals [2]. These pioneers recognised that carbonic acid converts into bicarbonate all non volatile mineral bases not bound by mineral acids and determined therefore that bicarbonate represents the alkaline reserve of the body [3]. They advocated that bicarbonate, measured at standard  $p\text{CO}_2$ , should be a physiological constant, and showed how well this measures acidosis caused by increased production or decreased elimination of organic acids, i.e. diabetic ketoacidosis and nephritis respectively [4].

However, they noted that bicarbonate given to diabetic patients improved their low plasma bicarbonate, but not their high urine acid excretion, measured as urine titratable acid plus ammonia [5]. They also recognised that increasing  $p\text{CO}_2$  caused chloride to shift into cells increasing plasma titratable alkali [6]. Despite these indications that changing mineral base influences pH, their theory based on the assumption that mineral base is fixed, has become our dogma.

Standard acid base teaching uses the Henderson-Hasselbalch equation to interpret blood gases, identifying acidosis or alkalosis caused by abnormalities in carbonic acid, measured from  $p\text{CO}_2$  and referred to as the respiratory component, or by abnormalities in bicarbonate, calculated in the blood gas analyser and referred to as the metabolic component.

Most clinicians consider bicarbonate to be the base that buffers carbonic and organic acids in the body, particularly since sodium

bicarbonate is used to treat metabolic acidosis. As a weak acid controlled by respiration, carbonic acid is the most important buffer diminishing pH change in response to acid/alkaline load, but bicarbonate cannot be the base that actually neutralizes organic and carbonic acids, accounting for the slightly alkaline blood pH of 7.4.

In 1978 Kildeberg and Winters presented the theory of net base balance describing how carbonic acid and organic acids, such as lactic acid, produced by metabolism are instead neutralised in the body by mineral base, measured as the excess of mineral cations over anions [7]. This allows the metabolic components of acid base balance to be identified. Metabolic acidosis with low bicarbonate may be an organic acidosis caused by high organic acid levels (lactic acidosis) or a mineral acidosis caused by low mineral base levels (hyperchloraemic acidosis), whereas metabolic alkalosis with high bicarbonate can only be caused by a mineral alkalosis with high mineral base levels (hypochloraemic alkalosis), because organic acid levels are normally low.

The Henderson-Hasselbalch equation no longer takes centre stage and instead of considering bicarbonate to be a base, it is used as a measure of the amount of carbonic acid that has dissociated to release hydrogen ions, in the same way that sodium measures the sodium hydroxide concentration, chloride the hydrochloric acid concentration and lactate the lactic acid concentration. Sodium bicarbonate corrects a mineral acidosis, but not an organic acidosis, by allowing a strong base, sodium hydroxide, to be given with a weak acid, carbonic acid, that is eliminated by respiration.

The theory of net base balance had in fact been recognised much earlier by Shohl and Sato, while working with Gamble at Johns Hopkins in 1921, when they investigated the effect of adding hydrochloric acid or sodium bicarbonate to the normal diet of three male infants, by meticulously performing 3 day mineral base balance studies [8]. In 1945 Darrow et al reported that healthy preterm infants

develop hyperchloraemic metabolic acidosis when fed Protein Milk Powder, providing 5.7 mmol of chloride compared to 2.0 mmol of sodium per 100 kcal. Balance studies confirmed that the acidosis was caused by the retention of more chloride than sodium [9].

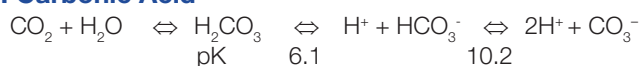
In 1970 urine net hydrogen ion excretion in preterm infants was reported to be low in the first 3 days compared to term infants [10] and then to increase with postnatal age from 1 to 4 weeks following the time course of their metabolic acidosis [11]. In one of these studies, metabolic acidosis was clearly shown to be due to the retention of chloride in excess of sodium for the first 14 days, but this finding was not recognised at the time or later [12]. Reports of metabolic acidosis in infants given Total Parenteral Nutrition (TPN) showed that the tendency to cause acidosis was related to how much more chloride than sodium TPN regimens contain, but once again this finding was not recognised at the time or later [13,14].

This article describes how mineral base balances carbonic and organic acids. The following article presents 3 prospective cohort studies of mineral balance and arterial blood gases in preterm infants receiving TPN which show that the composition of parenteral fluids, renal function and the rate of protein catabolism affect mineral base and organic acid, thereby accounting for the acid base status of these infants.

## THE THEORY OF ACID BASE BALANCE

Change in blood pH depends on change in the concentrations in mmol/L of three categories of acids and bases in plasma and extracellular fluid (ECF).

### 1. Carbonic Acid



Carbon dioxide, produced by aerobic metabolism and eliminated via the lungs, circulates in blood at a concentration controlled by the respiratory system, where it reacts with water to form carbonic acid. Blood gas analysers measure pH, PCO<sub>2</sub> and PO<sub>2</sub> and calculate bicarbonate from the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK} + \log \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} \quad \text{where pK} = 6.1$$

$$[\text{H}_2\text{CO}_3] = \text{pCO}_2 \text{ (mmHg)} \times 0.0306$$

The respiratory component of acid base balance is determined by PCO<sub>2</sub>. Bicarbonate measures the amount of carbonic acid that has dissociated to release hydrogen ions with negligible amounts of carbonate formed at blood pH.

The metabolic component is measured by base excess, defined as the amount of acid or base needed to restore pH to 7.4 at a normal pCO<sub>2</sub> of 40mmHg and temperature 37°C. The measurement least influenced by acute changes in pCO<sub>2</sub> is extracellular fluid base excess, which blood gas analysers calculate from pH and bicarbonate using experimentally determined formulae, describing the buffering capacity of blood and ECF, given in the Siggaard-Andersen Curve Nomogram [15].

### 2. Mineral Base

$$\text{Mineral base} = [\text{Na} + \text{K} + 2\text{Ca} + 2\text{Mg}] - [\text{Cl} + 1.8 \text{PO}_4]$$

Mineral base is measured as the excess of mineral cations over anions. Phosphate has an average negative charge of 1.8 at pH of 7.4 determined from the equation:

$$\text{pH} = \text{pK} + \log \frac{[\text{HPO}_4^-]}{[\text{H}_2\text{PO}_4^-]} \quad \text{where pK} = 6.8$$

The measurement of mineral base has an inherently large standard error, ± 2.3 mmol/L, mainly due to the ± 1 mmol/L error in measuring sodium and chloride.

The mineral base concentration of plasma reflects that of ECF, which is determined by the ECF content of mineral base divided by the ECF volume.

Change in the ECF content of mineral base depends on the balance

of mineral base, measured as intake – urine + stool + sweat output in mmol/kg/day, and on the retention of mineral base in cells or bone.

Change in ECF volume depends on change in water balance, measured simply as change in weight, and on change in the fraction of body weight made up by ECF (ECF fraction).

A model has been described to analyse these changes in preterm babies given TPN, from measurements of plasma mineral concentrations and weight at the beginning and end of balance periods, during which the external balance of minerals was measured as intake minus urine output, ignoring stool and sweat losses as insignificant [16].

Calcium, phosphate, potassium and magnesium are largely present in bones and cells. Virtually all calcium is in bone, which contains calcium and phosphate in a molar ratio of 10:6 [17].

Under stable conditions, with no change in plasma K, Ca, Mg or PO<sub>4</sub>, the rates at which these minerals enter and leave ECF are equal and so they do not contribute to change in ECF mineral base content. Instead they contribute to bone mineral base retention and soft tissue mineral base retention. These may be measured as follows, if the small amounts of intracellular sodium and chloride are ignored.

$$\begin{aligned} \text{Bone mineral base retention} &= 0.92 \times \text{Ca retention} \\ \text{Soft tissue PO}_4 \text{ retention} &= \text{PO}_4 \text{ retention} - 0.6 \times \text{Ca retention} \\ \text{Soft tissue mineral base} &= \text{K retention} + 2 \times \text{Mg retention} - 1.8 \\ &\quad \times \text{Soft tissue PO}_4 \text{ retention} \end{aligned}$$

Sodium and chloride are largely confined to ECF in the body and change in their plasma concentrations are determined by changes in weight, ECF fraction and external balance. Therefore, under stable conditions, change in the ECF content of mineral base can be measured simply as follows:

$$\begin{aligned} \text{Change in ECF content} &= \text{Na balance} - \text{Cl balance} \\ \text{of mineral base} &= [\text{Na intake} - \text{Cl intake}] - [\text{Na urine} - \text{Cl urine}] \\ &\quad \text{when stool and sweat losses are negligible.} \end{aligned}$$

### 3. Organic Acid

Metabolisable acid makes up the anion gap and, from the law of electroneutrality, plasma metabolisable acid can be measured as follows:

$$\text{Metabolisable acid} = \text{Mineral base} - \text{Bicarbonate}$$

Under normal circumstances, protein anion makes up more than half of metabolisable acid in plasma, where it provides colloid osmotic pressure necessary to balance hydrostatic pressure in tissue circulation. Because the protein concentration of interstitial fluid is very low, change in protein anion contributes little to change in metabolisable acid in ECF, which instead is determined by change in plasma non-protein metabolisable acid, or more simply organic acid, measured as follows:

$$\text{Organic acid} = \text{Mineral base} - \text{Bicarbonate} - \text{Protein anion}$$

$$\text{Protein anion} = (\text{pH} - 5.08) \times 0.104 \times \text{Protein concentration (g/L)}$$

The equation for measuring protein anion assumes an albumin: globulin ratio in plasma of 1.6:1 [18]. In fact the ratio in preterm babies is around 2:1, but this difference changes the calculation of protein anion very little. When measuring organic acid, the charge on phosphate should in principle be corrected for the actual pH rather than 7.4, just as the charge on bicarbonate and protein anion are calculated according to the actual pH. However once again this changes organic acid little, much less than the error of measuring mineral base.

The organic acids in plasma are normally produced in small amounts by body tissues. Some of these are the intermediary products of metabolism, such as lactate, pyruvate, free fatty acids and ketones. These are cleared from plasma partly by being taken up

and metabolised by other tissues particularly the liver, and partly by being excreted by the kidneys. Other organic acids are the end products of protein or purine catabolism, such as sulphate and urate respectively, and these must be eliminated in the urine since they cannot be metabolised further. As a rule organic acids are freely filtered through the glomeruli and not reabsorbed by the renal tubules.

The normal plasma concentrations of these organic acids during the first week after birth in healthy term infants, well preterm and small for gestational age babies are shown in [Table/Fig-1]. There is little data regarding sulphate. In preterm babies 3-10 days old, urine sulphate excretion is about 0.15mmol/kg/day [31], which would give a plasma sulphate concentration of 0.15mmol/L at a normal glomerular filtration rate of 1.0 L/kg/day. Other organic acids, such as acetate, citrate, gluconate, oxalate, nitrate, bile acids and conjugated bilirubin, are normally present in trace concentrations below 0.1mmol/L, similar to the concentrations of trace cations, such as iron, zinc and copper [32]. Ignoring trace anions, plasma organic acid levels in healthy term infants, calculated as the sum of measured values corrected for anion charge, is 5.3 mmol/L at 1-6 hours, falling to 4.9 mmol/L at 24-48 hours and 3.5 mmol/L at 7 days, with somewhat higher concentrations in well preterm babies, as shown in [Table/Fig-1].

Organic acid mmol/L	1-6 hours	24-48 hours	7 days	Infants	Ref
Lactate (arterial)	1.50±0.50 2.40±0.70	1.00±0.15 1.70±0.50	0.90±0.25	Term Preterm	[19, 20]
Pyruvate	0.15±0.03	0.13±0.02	0.12±0.03	All	[19, 21]
Free fatty acids	1.41±0.34 1.23±0.51 1.52±0.37	1.00±0.32 1.36±0.68 0.50±0.20	0.86±0.22	Term Preterm SGA	[21, 22, 23, 24]
Ketones	0.43±0.33 0.15±0.15	0.90±0.40 0.10±0.06	0.44±0.21	Term SGA	[22, 25, 26]
β-OH butyrate	0.29±0.20 0.17±0.12 0.26±0.19			Term Preterm SGA	[21]
Acetoacetate	0.05±0.05 0.03±0.03 0.04±0.03			Term Preterm SGA	[21]
Urate	0.31±0.09 0.36±0.13 0.46±0.16	0.32 0.16-0.57 0.41±0.14	0.20 0.14-0.34 0.17±0.05	Term 34-37wk 29-33wk	[27, 28, 29]
Sulphate	0.47 0.29-0.95		0.15	Term Preterm	[30, 31]
Acetate citrate gluconate others	Trace				[32]
TOTAL	5.27±1.59 6.30±2.07	4.93±1.33	3.46±1.06	Term Preterm	

**[Table/Fig-1]:** Normal plasma concentrations in mmol/L of organic acids in healthy term, preterm and small for gestational age (SGA) newborns during the first week. Total organic acid takes into account negative charge of 2 on sulphate and 3 on urate

The standard error of organic acid calculated by the difference between mineral base and bicarbonate is large, like that of mineral base. However whatever the error in measuring mineral base, the base excess is mathematically equivalent to subtracting the deviation in calculated organic acid from normal from the deviation in measured mineral base from normal.

## NORMAL ACID BASE BALANCE

Acid base balance is regulated by the respiratory system, which controls the rate of CO<sub>2</sub> elimination to match varying rates of CO<sub>2</sub> production thereby keeping PCO<sub>2</sub> normal, and by the kidneys, which control the rate of mineral base excretion to maintain the appropriate plasma mineral base concentration to keep bicarbonate normal. The appropriate plasma mineral base to achieve normal

bicarbonate of 24.5 mmol/L, at normal pH of 7.4 and PCO<sub>2</sub> of 40 mmHg, and at normal organic acid of 3.5 mmol/L, depends on the protein level and is given by the following equation:

$$\text{Normal mineral base} = 28 + 0.241 \times \text{Protein (g/L)}$$

The degree of abnormality of a particular mineral base concentration is measured as follows:

$$\text{Mineral base deviation} = \text{Actual mineral base} - \text{Normal mineral base.}$$

The factors determining urine mineral base excretion are readily appreciated by applying the law of electroneutrality to urine cations and anions as follows:

$$\text{In urine Mineral base} = \text{Organic acid} + \text{Bicarbonate} - \text{Ammonium.}$$

When measuring urine mineral base, the charge on phosphate should be corrected for urine pH, which varies over a wide range. In this equation organic acid is the excess of organic acids over organic bases, normally present only as creatinine, which is corrected for when titrating urine organic acid [33,34].

Plasma organic acid affects the rate of mineral base excretion, because filtered organic acids are not reabsorbed and must be accompanied by cations in the urine. The kidneys control the rate of mineral base excretion, to accommodate to varying rates of carbonic or organic acid production, by varying the rate of hydrogen ion secretion, formed from carbonic acid in renal tubular cells. High rates of hydrogen ion secretion completely reabsorb filtered bicarbonate and increase ammonium excretion, formed by the reaction of hydrogen ions with glycine and glutamine in renal tubular cells. This decreases mineral base excretion and makes urine acid. Low rates of hydrogen ion secretion do not fully reabsorb filtered bicarbonate, which is therefore excreted with little ammonium. This increases mineral base excretion and makes urine alkaline.

## ACID BASE ABNORMALITIES

The cell membrane anion exchange mechanism allows bicarbonate, chloride, phosphate and organic anions to interchange across cell membranes according to the Gibbs-Donnan law of equilibrium [6,35-39]. An increase in any of these anions results in a reciprocal fall in the other anions. By this mechanism, cell proteins and organic acids, which are weak acids, participate as buffers diminishing change in extracellular pH resulting from acid base abnormalities.

Carbonic and lactic acidosis both produce cell chloride uptake, which increases extracellular mineral base reducing pH change. Furthermore changes in carbonic acid cause inverse changes in lactic and organic acids, which again reduce pH change. While high carbonic acid protects intracellular pH by producing low lactic and organic acids, the converse, low carbonic acid exposes the cells to the risks of high lactic and organic acids. Replacing carbonic acid, a very weak acid with lactic acid, a stronger acid with a pK of 3.86, or sulphuric acid, a very strong acid, may adversely affect cell function.

The cell membrane Na/K and other ion exchange mechanisms do not alter acid base balance [16,36].

Accumulation of carbon dioxide and lack of oxygen are the two most important causes of acid base disturbance in clinical practice. These two processes affect the distribution of the major acids and bases in the body differently, because of different effects on cell adenosine tri-phosphate (ATP) supplies.

## ACCUMULATION OF CARBON DIOXIDE

When lung abnormalities interfere with the elimination of carbon dioxide, carbonic acid accumulates in cells and extracellular fluid. Tissue oxygen delivery is maintained by oxygen and ventilator therapy with preserved cardiac function assisted by vasodilation caused by hypercapnoea. Cell ATP levels are sustained, allowing lactic and organic acids to fall to very low levels, which, together

with the increase in extracellular mineral base caused by cell chloride uptake, reduces the fall in pH as carbon dioxide accumulates. The kidneys increase renal tubular hydrogen ion secretion, and over a few days extracellular mineral base rises further, partly correcting the respiratory acidosis.

## LACK OF OXYGEN

By contrast impaired cardiac function or loss of blood volume may decrease oxygen delivery to tissues causing shock, which prevents aerobic metabolism. Cell ATP levels diminish despite the modest contribution from anaerobic metabolism, which generates lactic acid in increasing amounts in cells and extracellular fluid [40]. Bicarbonate falls as it is converted to carbonic acid, which is eliminated by hyperventilation, and cell chloride uptake increases extracellular mineral base, both reducing the drop in pH.

As cells consume ATP they release inorganic phosphate into extracellular fluid. Cell protein catabolism and blood glucose increase in an effort to maintain energy production [41-43] and this releases potassium from cells often in excess of phosphate [16], thereby further increasing extracellular mineral base. This rises even more when sodium bicarbonate or blood products containing sodium citrate are given to the patient. Whilst high mineral base diminishes the fall in blood pH caused by lactic acidosis, it does not improve tissue oxygenation. Shock impairs kidney function, preventing any compensatory increase in renal hydrogen ion secretion as well as the elimination of organic acids.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Oct 29, 2012**  
Date of Peer Review: **Jan 27, 2013**  
Date of Acceptance: **Aug 29, 2013**  
Date of Publishing: **Sept 10, 2013**