Basic sciences review

Acid-Base Balance: Part I. Physiology

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ABSTRACT

Objective: *To review the normal human acid-base physiology and the pathophysiology and management of acid-base disturbances in a two-part presentation.*

Data sources: *Articles and published peer-review abstracts and a review of studies reported from 1990 to 2000 and identified through a MEDLINE search of the English language literature on acid-base balance.*

Summary of review: *In a healthy individual the extracellular fluid pH change following addition of a metabolic acid or base, is modified initially by the body's buffers. Subsequent respiratory compensation, by excretion or retention of CO_2, modifies this change before metabolism of the organic acid or renal excretion of the acid or alkali returns the plasma bicarbonate to normal. A primary respiratory acid-base change is modified initially by cellular buffers, with renal compensatory mechanisms adjusting slowly to this change. However, correction of the respiratory pH disorder only occurs with correction of the primary disease process.*

Conclusions: *In man the acid-base balance is maintained and regulated by the renal and respiratory systems, which modify the extracellular fluid pH by changing the bicarbonate pair (HCO_3^- and PCO_2); all other body buffer systems adjust to the alterations in this pair.* (**Critical Care and Resuscitation 2001; 3: 181-187**)

Key words: Acid-base balance, metabolic acidosis, metabolic alkalosis

By affecting the charge on reactive groups of enzymes within the extracellular and intracellular fluids of the living organism, chemical reactions are influenced by the prevailing pH.[1] Despite the abundance of hydrogen in body fluids, the concentration or chemical activity of the H^+ ion (or hydronium ion H_3O^+) is remarkably small and constant. This is largely due to the presence of buffer systems which allow for a rapid turnover of protons to take place with minimal alteration in H^+ ion activity.

DEFINITIONS

In general, the definitions suggested by the Ad Hoc Committee of the New York Academy of Sciences have been adopted.[2]

pH. Is the negative logarithm of the H^+ ion activity (Ha^+), which is equal to the H^+ ion concentration when the activity coefficient is unity. The pH is measured using a glass-membrane electrode porous only to H^+ ions. A transmembrane potential develops which is proportional to the log of the H^+ ion activity (Ha^+). This potential is compared with the potential recorded using the glass electrode and a standard solution of selected pH value.

Within the physiological range of pH values in man, the H^+ ion activity coefficient is unity, therefore the measurement of H^+ provides an accurate and practical scale of acidity and alkalinity, when compared with its logarithmic counterpart of pH.[3] For example, it allows one to use the Henderson equation to assess clearly the

acid-base consequences of alteration in the PCO_2 and HCO_3^- values:[4]

$$[H^+] = K \times \frac{CO_2}{[HCO_3^-]}$$

The plasma concentration of the H^+ ion at a pH of 7.4 is 40 nmol/L. Doubling or halving the H^+ concentration, reduces or increases the pH by $\log_{10} 2$, respectively (i.e. by approximately 0.3). Therefore,

pH	H^+ nmol/L
6.8	160
7.1	80
7.4	40
7.7	20

Acid. A proton donor or H^+ ion donor.

Base. A proton acceptor or H^+ ion acceptor.

Acidaemia. Arterial blood pH less than 7.36 ($H^+ > 44$ nmol/L).

Alkalaemia. Arterial blood pH greater than 7.44 ($H^+ < 36$ nmol/L).

Acidosis. An abnormal process or condition which tends to lower the arterial pH if there are no secondary changes in response to the primary disease process.

Alkalosis. An abnormal process or condition which tends to raise the arterial pH if there are no secondary changes in response to the primary disease process.

A mixed disorder. Two or more primary acid-base abnormalities coexist.

Compensation. Refers to normal body processes that tend to return the arterial pH to normal (e.g. respiratory or renal).

Acid-base balance. Refers to the difference in quantity between input and output of acids and bases (Table 1).

Table 1.   Daily H^+ balance

	Input mmol/day		Output mmol/day
Volatile			
Carbon dioxide	13 000	Lungs	13000
Lactate	1 500	Liver, Kidney	1500
Nonvolatile			
Protein (SO_4)	45	Titratable acid	30
Phospholipid (PO_4)	30	Ammonium	40
Other	12		

Buffer. A solution containing substances that have the ability to minimise changes in the pH when an acid or base is added to it.

pKa. The negative logarithm of the dissociation constant. If it describes a buffer system, then it is numerically equal to the pH of the system when the acid and its anion are present in equal concentrations.

Strong ions. An analysis of acid-base chemistry has been proposed based on the law of electroneutrality in aqueous solutions, where the total number of cations must equal the total number of anions.[5,6] The central tenet to the analysis is that only the independent variables, which are the strong ions (e.g. sodium, potassium, calcium, magnesium, chloride and organic anions), PCO_2 and the non-volatile weak acids (A_{TOT} = HA + A^- and in plasma is predominantly the albuminate ions), can change acid-base status, as they change the dependent variables of H^+ and HCO_3^- to maintain electrical neutrality.

The metabolic acid-base abnormality is characterised by calculating the strong-ion difference (or SID = $[Na^+ + K^+ + Ca^{2+} + Mg^{2+}] - [Cl^- + lactate]$), a value which is essentially equal to the sum of the bicarbonate and albuminate ions,[7] (i.e. HCO_3^- = SID - A^-) and similar to the buffer base described by Singer and Hastings more than 50 years ago.[7-9]

This approach has not been helpful in clinical practice (e.g. it leads to the misconceptions that a saline induced dilution acidaemia is due to an increase in Cl^- rather than a decrease in $HCO3^-$, or an elevated or reduced plasma albumin level may lead to metabolic acidosis and metabolic alkalosis, respectively).[10-12]

REGULATION OF pH [H^+] IN BODY FLUIDS

In man, despite wide variations in dietary acid and base, there is no specific centre for H^+ ion regulation. The body's respiratory and renal systems coordinate to regulate H^+ homeostasis by regulating HCO_3^- and PCO_2. The initial body defense against a change in pH is carried out by the body's buffer systems.[13]

BODY BUFFERING

Dilution

If one compares the effect of adding the daily nonvolatile H^+ load (i.e. 70 mmol H^+) to a 70 kg man and to an equal volume of non-buffered water, at the same temperature and pH (e.g. table 2), it is clear that dilution is a poor defense against pH changes.

Buffer systems

These are present in the extracellular fluid (ECF) and intracellular fluid (ICF). Their effectiveness, or capacity, is proportional to the amount of buffer, the

pKa of the buffer, the pH of the carrying solutions and whether the buffer operates as an open or closed system.

Table 2. Effect of adding daily nonvolatile H^+ load to man and to an equivalent volume of nonbuffered water

	Water volume (L)	pH (H^+ nmol/L) Before	After
70 kg man	42	7.4 (40)	7.39 (41)
Water	42	7.4 (40)	2.78 (1 666 666)

Buffer mechanisms

Any chemical reaction reaching an equilibrium can be expressed by the law of mass action. In the case of a weak acid:

$$HA \square [H^+] + [A^-] \qquad (1)$$
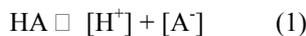
at equilibrium the product of the concentrations of H^+ and A^- is a constant fraction of the concentration of HA or:

$$K = \frac{[H^+][A^-]}{[HA]} \qquad (2)$$

The value of K at equilibrium is always the same and independent of the concentrations of the reactants that are present initially. With the addition of another acid (i.e H^+ donor) to the system, the ionisation of the weak acid HA is reduced (to keep K constant). If a base is added, the reduction in the H^+ ion concentration produces further ionisation of the acid, HA. Both reduce the change in H^+ ion concentration (pH).

However, as the ionisation of a weak acid is small, only a small addition of H^+ can be tolerated before the pH falls. By supplementing the ion A^- with the addition of a salt of a strong base (e.g. NaA), this acts as a reservoir of A^- for combining with the added H^+.

Therefore, a buffer system can be produced by mixing a weak acid with the salt of that acid and a strong base. Equation (2) can be rearranged as:

$$[H^+] = K \times \frac{[HA]}{[A^-]} \qquad (3) \text{ Henderson equation}$$

The negative log of equation (3) is:

$$pH = pKa + \log \frac{[A^-]}{[HA]} \qquad (4) \text{ Henderson-Hasselbalch equation}$$

From equation (4) it can be seen that the pH of 1 L of a weak acid solution with a pKa of 7.0 which has a concentration of 5.5 mmol/L of $[A^-]$ and 5.5 mmol/L of HA, is 7.0. If 0.5 mmol of a strong acid is added to this solution, $[A^-]$ will combine with the free $[H^+]$ to form HA (i.e the concentration of $[A^-]$ will decrease to 5 mmol/L and the concentration of HA will increase to 6 mmol/L) and the pH will decrease to 6.92. If 4.5 mmol of a strong acid are added to the solution, the concentration of $[A^-]$ will decrease to 1 mmol/L, the concentration of HA will increase to 10 mmol/L and the pH will fall to 6.0. However, addition of more acid reduces the pH dramatically (e.g. the addition of an extra 0.9 mmol of acid will decrease the pH to 5 and the addition of an extra 0.999 mmol of acid will decrease the pH to 3). So most (i.e. 80%) of the buffering occurs within $\pm$ 1 pH unit of the pKa value of the buffer system (Fig. 1), which occurs when,
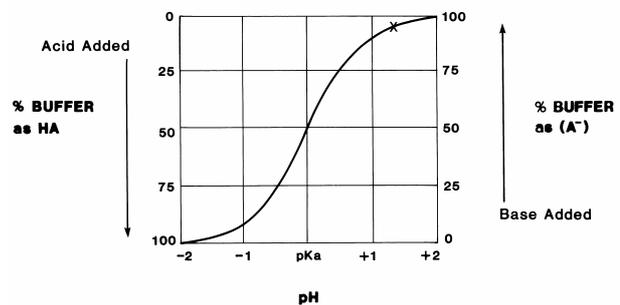

Figure 1. Reaction curve for the buffer HA:[A⁻] where pH = pKa $\pm$ 2. (After Guyton AC. Textbook of medical physiology. 4th Ed, WB Saunders & Co, Philadelphia. 1971).

$$\log \frac{[A^-]}{HA} \text{ is } \pm 1 \text{ i.e.,} \qquad \frac{BASE}{ACID} \quad \frac{10}{1} \text{ or } \frac{1}{10}$$

The major body buffer systems involve bicarbonate, protein, haemoglobin and phosphate.

Bicarbonate-carbonic acid buffer pair. The arterial H^+ ion activity can be represented by the Henderson equation:

$$[H^+] = 24 \times \frac{PaCO_2}{[HCO_3^-]}$$

or the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{PaCO_2 \times 0.03}$$

Where:

24	=	the numerical value of the solubility coefficient of carbon dioxide and the dissociation constant of carbonic acid.
$PaCO_2$	=	arterial blood partial pressure in mmHg
$[HCO_3^-]$	=	arterial blood bicarbonate concentration in mmol/L
$[H^+]$	=	arterial blood H^+ ion concentration in nmol/L

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0.03   =   solubility coefficient of carbon dioxide
6.1   =   negative logarithm of the dissociation constant of carbonic acid

This system is quantitatively the most important ECF buffer, and functions better as a physiological (or open) buffer than chemical (or closed) buffer. Its pKa is 6.1, therefore its chemical buffering capacity at a pH of 7.4 is poor (see position x in figure 1).

The benefit of an open, rather than closed, buffer system can be demonstrated if both systems are subjected to a pH change of 0.3 units by the addition of an acid. If one considers the Henderson-Hasselbalch equation under normal conditions, when pH 7.4, $PaCO_2$ 40 mmHg, HCO_3^- 24 mmol/L, then:

$$7.4 = 6.1 + \log \frac{24}{1.2}$$

However, addition of an acid to decrease the pH by 0.3 units, will produce different effects in the closed system when compared to the open system. For example,

A closed buffer system   *An open buffer system*

$$7.1 = 6.1 + \log \frac{22.9}{2.29} \qquad 7.1 = 6.1 + \log \frac{12}{1.2}$$

In both systems the ratio of H_2CO_3 to HCO_3^- remains constant. In the closed system the total amount of H_2CO_3 and HCO_3^- remains constant (i.e. 25.2 mmol/L). In the open system, the denominator only is kept constant at 1.2 mmol/L, by increasing the ventilation and keeping the $PaCO_2$ at 40 mmHg ($40 \times 0.03 = 1.2$). The buffer anion in the closed system falls from 24 to 22.9 whereas in the open system it falls from 24 to 12, thereby buffering more H^+.

The bicarbonate/carbonic acid system also has the added advantage of a further carbon dioxide change with respiratory compensation, reducing even further the pH defect. These responses are shown, in stages, in figure 2.

The utility of this buffer system can be fully appreciated when it is realised that it is 'open ended' for both the numerator and the denominator. The $PaCO_2$ can be modified by a change in ventilation, and the HCO_3^- concentration can be regulated by renal mechan-isms. All other buffer systems in the body adjust accordingly to alterations in this pair, an interrelation-ship which is termed the isohydric principle.

Haemoglobin, protein and phosphate buffers.
Proteins have a series of titratable groups within their molecular structure with the ability to buffer pH changes. The buffering characteristic of haemoglobin is almost entirely dependent upon the imidazole group of histidine, which dissociates less when haemoglobin is in the oxygenated form compared with the deoxygenated form. Thus, deoxygenated blood is a better buffer than oxygenated blood; the haemoglobin molecule accomm-odates 0.7 mmol of H^+ for each mmol of oxygen released, without any change in pH. As the respiratory quotient is normally 0.8, a slight reduction in pH usually occurs when blood travels from the arterial to the venous system.
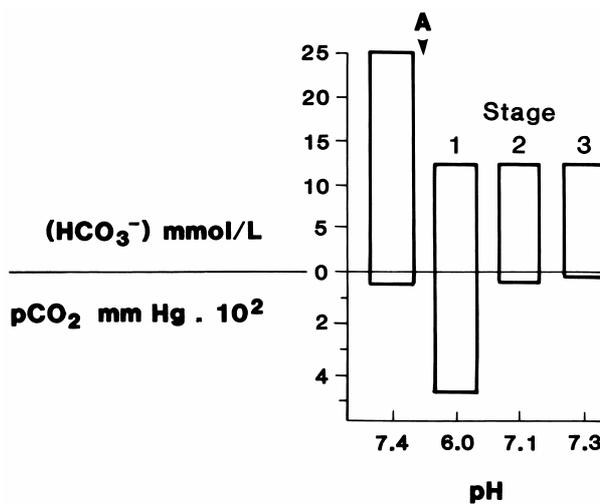

Figure 2. Bicarbonate buffer system in blood (in vitro) if acid were added at **A** to reduce plasma HCO_3^- by 50%. The histograms represent buffering if it were to occur in 3 separate stages. Stage 1 represents chemical buffering only, stage 2 represents the added effect of maintaining pCO_2 constant, and stage 3 represents the compensatory reduction in pCO_2 in response to the acid load. (After Gamble JL. Chemical anatomy, physiology and pathology of extracellular fluid. 6th Ed. Harvard University Press, Massachusetts 1951).

The haemoglobin buffer is an important one, as it is involved in handling the largest daily acid load of the body, i.e. carbonic acid. Gram for gram, plasma proteins have one-third the buffering capacity of haemoglobin; however, as haemoglobin has twice the concentration of plasma protein, it has six times the capacity to buffer H^+.

The phosphate buffer system has a pKa of 6.8 and so is a better chemical (or closed) buffer system than the bicarbonate buffer system. However, in plasma it has one-twentieth the concentration of bicarbonate, and also operates only as a closed system, so its capacity is far less than that of the bicarbonate-carbonic acid buffer. In the ICF and in urine, the phosphate buffer system assumes greater importance.

Total Body Buffering
The contributions of ICF and ECF buffers vary depending upon the nature, severity and duration of the

acid or base disturbance. In dogs in which respiratory or metabolic acid-base defects were produced, the respiratory pH changes were buffered mainly by ICF buffers, whereas metabolic pH changes had a greater ECF buffering component (Figure 3).[14-16] Preferential utilisation of extracellular buffers occurs in the initial phase of a metabolic acidosis with the contribution of ICF buffers becoming greater as the acidosis increases in severity.[17]
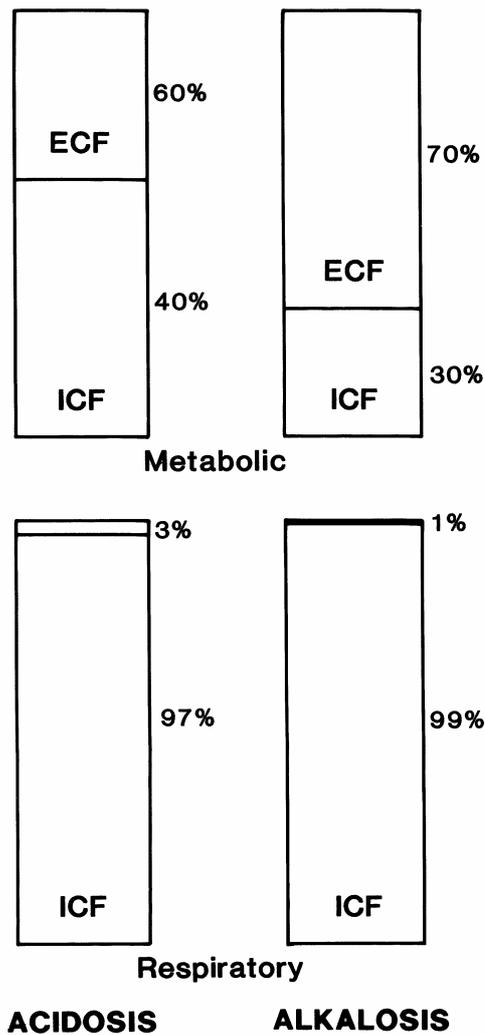

Figure 3. Buffering contributions of the intracellular fluid (ICF) and extracellular fluid (ECF) with primary respiratory or metabolic acid-base changes. (After Pitts RF. Physiology of the kidney and body fluids 2nd Ed. Year Book Medical Publishers, Chicago. 1968).

Experiments using rat diaphragm and human leucocytes reveal that conditions simulating respiratory acidosis or alkalosis produce a greater ICF pH change than do conditions simulating metabolic acidosis or alkalosis.[18-20] Furthermore, when metabolic acidosis or

alkalosis are simulated and appropriate respiratory compensatory (i.e. carbon dioxide) changes are also included, the ICF pH remains remarkably constant, suggesting that there is a greater *in vivo* tolerance to metabolic pH change than there is to respiratory pH change.[18,21,22] Although, studies in animals with severe respiratory acidosis (e.g. PCO_2 values up to 200 mmHg), the ICF pH is usually always greater than 6.8.[23]

RESPIRATORY RESPONSE

It is clear when considering the Henderson equation [Equation (1)], that variations in PCO_2 alter the pH. The effect is rapid and influences both the ICF and ECF. Arterial PCO_2 varies inversely with alveolar ventilation and directly with carbon dioxide production. Normal carbon dioxide production is 13,000 mmol per day; if pulmonary ventilation ceased in man for 20 min, $PaCO_2$ would rise to 110 mmHg (13.3 kPa) and pH would fall to 7.03. If renal function ceased for a similar period, no change in arterial pH would occur.

Regulation of ventilation involves a complex interplay between mechanical and chemical stimuli. Any change in arterial HCO_3^-, PCO_2, pH, PO_2 or stimuli from pulmonary mechanoreceptors alter ventilation and thus $PaCO_2$ and pH. The respiratory response to a metabolic pH change follows peripheral chemoreceptor stimulation, and provides the compensatory response to metabolic pH change.

RENAL RESPONSE

This determines the final outcome to the acid or base load, by altering the denominator of the Henderson equation (i.e. $[HCO_3^-]$). The response is slow and the maximum excretory capacity of 300 mmol H^+ can only be reached after 7-10 days.[24]

Unlike all other ions, HCO_3^- has no permanence. It may be generated from carbon dioxide and water or lost with carbon dioxide excretion. The accompanying H^+ generated or lost is dealt with by the body's buffers. The kidney uses the HCO_3^- ion for alkali reserve and as an anion for sodium reabsorption or excretion when maintaining the ECF volume; the lungs use the HCO_3^- ion for carbon dioxide transport and excretion.

Renal regulation of H^+ balance is due to reabsorption or excretion of filtered HCO_3^-, excretion of titratable acidity (TA) and excretion of ammonia. Tubular H^+ secretion usually involves Na^+ reabsorption, maintaining electrical neutrality.

Reabsorption (reclaiming) filtered HCO_3^-

About 85-90% of the filtered HCO_3^- is reclaimed by the proximal tubule. Further reabsorption occurs in the distal nephron, with the luminal fluid being free of HCO_3^- at a luminal pH of 6.2.[25] The amount of HCO_3^-

reaching the distal nephron is influenced by the filtered load of HCO_3^- (i.e. with a metabolic acidosis, the total proximal H^+ secretion is less than normal) and the functional ECF volume.[26] The mechanism of proximal tubular HCO_3^- reabsorption relies upon H^+ secretion.

Cellular carbonic anhydrase (CA) supplies H^+ for the hydrogen pump and the brush border CA facilitates the combination of HCO_3^- with H^+. In the absence of the brush border carbonic anhydrase, a disequilibrium pH of 0.85 - 1.0 occurs, and proximal H^+ secretion is inhibited.

Formation of titratable acidity

At a pH of 7.4, four fifths (80%) of the circulating phosphate is in the monohydrogen form and one fifth (20%) is in the dihydrogen form. The majority of the urinary titratable acidity (TA) is formed with the conversion of monohydrogen phosphate to dihydrogen phosphate, which occurs throughout the nephron.[25] The pKa of this system is 6.8, and at maximum urinary acidity (i.e. pH 4.5) almost all (99%) of the filtered phosphate is in the dihydrogen form. At this urinary pH, 74% of the filtered creatinine (pKa 4.97) and 92% of the uric acid (pKa 5.8) are in the nonionised mode, and may account for 25% of the urinary TA at maximum urinary acidity.

Normally, 20 - 30 mmol of H^+/day are excreted as TA, and this is proportional to the amount of buffer excreted, the pKa of the buffer, and the pH of the urine. In diabetic ketoacidosis the rate of excretion of unionised betahydroxybutyrate (pKa 4.8) with maximum urinary acidity is 66%; so, in this condition it forms a large component (e.g. up to 250 mmol H^+/day) of urinary TA. Acetoacetic acid has a pKa value of 3.8 and therefore only 17% is excreted at maximum urinary acidity, although as the beta-hydroxybutyrate:aceto-acetate ratio is usually 3:1 (which may increase up to 9:1 with reduced redox states) almost all of the urinary ketone excretion is in the form of betahydroxybutyric acid. Only 20% of lactic acid (pKa 3.9) remains in the nonionised state at maximum urinary acidity, therefore excretion of unionised lactic acid in lactic acidosis is also low.

Normally, urinary excretion of phosphate is determined by the need to maintain phosphate balance rather than acid-base homeostasis. Thus TA appears to play a supportive, rather than an active, role in H^+ balance.

Formation of ammonia

The major site for ammonia (NH_3) production is in the proximal convoluted tubule epithelium although it can be formed in tubular epithelia throughout the nephron.[27] Deamidation and deamination of glutamine accounts for 60% of the urinary NH_3 whereas 30 - 35%

comes from free arterial NH_3. The NH_3 diffuses into the renal tubular lumen where it binds a H^+ ion to form a non diffusible ammonium ion (NH_4^+) which is subsequently excreted.[28] This process permits Na^+/H^+ exchange to occur without further change in urinary pH, although an acidic urine allows a greater sink into which free NH_3 can diffuse and is therefore one of the determinants of urinary NH_4^+ excretion.

Renal tubular synthesis of NH_3 is coupled to renal gluconeogenesis which in turn is attuned to the body's acid-base requirements. Systemic acidosis, hypokalaemia and mineralocorticoids increase ammonia production.[27] Normally 30 - 50 mmol of H^+/day are excreted as NH_4^+, which may increase to 300 mmol/day in severe acidosis.

Mechanisms of proximal and distal H^+ secretion

Proximal H^+ secretion

This is a low-gradient (minimal luminal pH achievable is 7.0), high-capacity (its H^+ secretion is responsible for reabsorbing most of the filtered HCO_3^-, i.e. 4000 - 5000 mmol/day) system. The proximal H^+ secretion is increased with hypokalaemia, hypercapnia, increased luminal HCO_3^-, increased tubular Na^+ reabsorption, the presence of nonreabsorbable anions (e.g. SO_4^{2-}, NO_3^-, penicillin anion) and increase in carbonic anhydrase activity. In the presence of a functional ECF depletion, nonreabsorbable anion or metabolic alkalosis, the Na^+/H^+ exchange mechanism is exaggerated, maintaining the ECF volume at the expense of pH homeostasis. Thus the maximum HCO_3^- reabsorption capacity of the kidney (i.e. Tm HCO_3^-) is not a fixed value and varies in response to the above factors.[26]

Distal H^+ secretion

This is a high-gradient (minimal luminal pH achievable is 4.5), low-capacity (H^+ secretion ranges from 0 - 300 mmol/day) system. Unlike the proximal tubule the distal nephron is influenced by mineralocorticoid activity. In hyperaldosteronism, distal Na^+ reabsorption and excretion of H^+ and K^+ are enhanced. In the presence of hypokalaemia, H^+ loss is augmented due to electroneutrality requirements for some of the distal Na^+ reabsorbed. In secondary hyperaldosteronism, the K^+ and H^+ losses may be less than in primary hyperaldosterone states, due to a reduction in distal luminal flow induced by avid proximal Na^+ reabsorption. Thus an increase in distal H^+ or K^+ urinary secretion may only become evident when distal Na^+ delivery is increased, for example with the use of diuretics or the administration of a sodium salt of a non reabsorbable anion.

REFERENCES

1. Relman AS. Metabolic consequences of acid-base disorders. Kidney Int 1972;1:347-359.
2. Anderson OS, Astrup P, Bates RG, et al. Report of ad hoc committee on acid-base terminology. Ann NY Acad Sci 1966;133:251-253.
3. Campbell EJM. RIpH. Lancet 1962;i:681-683.
4. Henderson LJ. The theory of neutrality regulation in the animal organism. Amer J Physiol 1908;21:427-448.
5. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444-1461.
6. Fencl V, Leith DE. Stewart's quantitative acid-base chemistry: applications in biology and medicine. Respir Physiol 1993;91:1-16.
7. Siggaard-Andersen O, Fogh-Andersen N. Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. Acta Anaesthesiol Scand Suppl 1995;107:123-128.
8. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine (Baltimore) 1948;27:223-242.
9. Wooten EW. Analytic calculation of physiological acid-base parameters in plasma. J Appl Physiol 1999;86:326-334.
10. Worthley LIG. Strong ion difference: a new paradigm or new clothes for the acid base emperor. Critical Care and Resuscitation 1999;1:211-214.
11. Siggaard-Andersen O, Fogh-Andersen N. Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. Acta Anaesthesiol Scand Suppl 1995;107:123-128.
12. Asano S, Kato E, Yamauchi M, Ozawa Y, Iwasa M. The mechanism of acidosis caused by infusion of saline solution. Lancet. 1966; i: 1245-1246.
13. Worthley LIG. Hydrogen ion metabolism. Anaesth Intens Care 1977;5:347-360.
14. Giebisch G, Berger L, Pitts RF. The extrarenal response to acute acid base disturbances of respiratory origin. J Clin Invest 1955;34:231-245.
15. Swan RC, Pitts RF. Neutralization of infused acid by nephrectomized dogs. J Clin Invest 1955;34:205-212.
16. Swan RC, Axelrod DR, Seip M, Pitts RF. Distribution of sodium bicarbonate infused into nephrectomized dogs. J Clin Invest 1955;34:1795-1801.
17. Schwartz WB, Orning KJ, Porter R. The internal distribution of hydrogen ions with varying degrees of metabolic acidosis. J Clin Invest 1957;36:373-382.
18. Adler S, Roy A, Relman AS. Intracellular acid-base regulation, II The interaction between CO_2 tension and the extracellular bicarbonate in the determination of muscle cell pH. J Clin Invest 1965;44:21-29.
19. Relman AS. The participation of cells in disturbances of acid-base balance. Ann N Y Acad Sci 1966;133:160-171.
20. Levin GE, Collinson P, Baron DN. The intracellular pH of human leucocytes in response to acid-base changes in vitro. Clin Sci 1976;50:293-299.
21. Schwartz WB, Brackett NC Jr, Cohen JJ. The response of extracellular hydrogen ion concentration to graded degrees of chronic hypercapnia: the physiological limits of the defense of pH. J Clin Invest 1965;44:291-302.
22. Adler S, Roy A, Relman AS. Intracellular acid-base regulation, I The response of muscle cells to changes in CO_2 tension or extracellular bicarbonate concentration. J Clin Invest 1965;44:8-20.
23 . Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? Am J Resp Crit Care Med 1994;150:1722-1737.
24. Sartorius OW, Roemmelt JC, Pitts RF. The renal regulation of acid base balance in man: The nature of renal compensations in ammonium chloride acidosis. J Clin Invest 1949;28:423-439.
25. Pitts RF. Physiology of the kidney and body fluids. 2nd Ed. Year Book Medical Publishers. Chicago 1968.
26. Seldin DW, Rector FC. The generation and maintenance of metabolic alkalosis. Kidney Int 1972;1:306-321.
27. Toto RD. Metabolic acid-base disorders. In Kokko JP, Tannen RL (eds). Fluids and Electrolytes. WB Saunders Co, Philadelphia, 1986, pp 229-304.
28. Pitts RF. The role of ammonia production and excretion in regulation of acid base balance. N Engl J Med 1971;284:32-38.