Review Article

The Stewart Approach – One Clinician's Perspective

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Abstract
Peter Stewart added controversy to an already troubled subject when he entered the clinical acid-base arena. His approach puts water dissociation at the centre of the acid-base status of body fluids. It is based on six simultaneous equations, incorporating the Laws of Mass Action, Mass Conservation, and Electrical Neutrality. Together with Gibbs-Donnan equilibria, these equations explain the diagnostically important $PaCO_2$/pH relationship, and improve understanding of the physiologic basis of traditional acid-base approaches. Spin-offs have included new scanning tools for unmeasured ions, in particular the 'strong ion gap' and 'net unmeasured ions'. The most controversial feature is the designation of pH and bicarbonate concentrations as dependent variables, answerable exclusively to three independent variables. These are the strong ion difference (SID), the total concentration of non-volatile weak acid (A_{TOT}), and PCO_2. Aspects of this assertion conflict with traditional renal physiology, and with current models of membrane H^+/base transporters, oxidative phosphorylation, and proton and bicarbonate ionophores. The debate in this area is ongoing. Meanwhile, Stewart-style diagnostic and decision support systems such as the 'Strong Ion Calculator' and the web-site www.acidbase.org are now appearing.

The Turbulent Pre-Stewart Era

When Peter Stewart entered the arena in the early 1980s, the application of acid-base physiology to blood gas interpretation was a notoriously controversial subject.[1] By that time most practitioners were tracking pH, rather than $[H^+]$. Many had accepted the arbitrary division of acid-base disorders into two broad categories, 'respiratory' and 'metabolic', with arterial PCO_2 ($PaCO_2$) the primary index of respiratory acid-base status. However, then as now, there was no universally accepted method of defining and quantifying the metabolic component.

In 1960, there had been a landmark development - the introduction of 'base excess' (BE) by Siggaard-Andersen and Engel.[2] Developed from a series of experiments on the blood of Danish volunteers, BE was promoted as the first genuine CO_2-invariant measure of metabolic acid-base status. During the subsequent debate,[3] most practitioners aligned themselves with one of two 'schools', Boston or Copenhagen. BE became the flagship of the Copenhagen school.

BE is usually defined as the concentration of titratable hydrogen ion required to return the pH of in vitro whole blood to 7.4 at 37 °C, with PCO_2 held at 40 mm Hg. The calculation requires simultaneous measurements of plasma pH, blood PCO_2 and haemoglobin concentration. For the first 17 years, this calculation was based on the original, experimentally-determined nomogram. Then Siggaard-Andersen published the Van Slyke equation,[4] using expressions linking plasma and intra-erythrocytic buffering and associated Gibbs-Donnan ionic distributions, and named in honour of the American acid-base pioneer Donald Dexter Van Slyke.

A useful version is as follows:

$$BE = \{[HCO_3^-] - 24.4 + (2.3 \times [Hb] + 7.7) \times (pH - 7.4)\} \times (1 - 0.023 \times [Hb])$$

where $[HCO_3^-]$ and pH are plasma values and [Hb] is the blood haemoglobin concentration expressed in mmol/L.

However, BE caused problems from the outset by failing to incorporate ion traffic across and beyond vascular boundaries. It became clear, that despite demonstrable invitro CO_2-invariance,[5] a primary $PaCO_2$ change in the living organism causes BE to move in the opposite direction.[6] The result is that

concurrent $PaCO_2$ disturbances distort the accuracy of the BE metabolic acid-base signal, in proportion to their severity. For an example of this phenomenon, refer to the Table, which is based on data from a patient with an exacerbation of chronic respiratory failure. Note that an acute $PaCO_2$ reduction from 172 mm Hg to 124 mm Hg increased BE by >4 mEq/L, despite an unchanged metabolic acid-base status.

Exploiting this flaw, the Boston school encouraged clinicians to abandon BE and switch to empiric 'rules of thumb'.[7] Derived from experimental and clinical in vivo data, these set out the observed $PaCO_2$ versus $[HCO_3^-]$ relationships in various acid-base perturbations. However, the need to commit six equations to memory (acute and chronic respiratory acidosis and alkalosis, metabolic acidosis and alkalosis), plus the bedside 'mental gymnastics' involved in their application,[3] were a disincentive. Moreover, being linear approximations of non-linear events, the Boston rules have limitations. For example, they cannot track the expected behaviour of $[HCO_3^-]$ in acute and chronic hypercapnia beyond a $PaCO_2$ of 80–100 mm Hg. The data in the Table illustrate this caveat, demonstrating that despite an acute $PaCO_2$ reduction of 50 mm Hg, $[HCO_3^-]$ remained unchanged because of the continuing severe hypercarbia.

Meanwhile, the Copenhagen school fought back with standard base excess (SBE),[8] also known as extracellular base excess (BE_{ECF}). SBE is BE calculated from the existing $PaCO_2$ and pH, but at a haemoglobin concentration of approximately 50 g/L to replicate the mean extracellular haemoglobin concentration. SBE does appear to have acceptable CO_2-invariance in vivo (again illustrated in the Table), although it is less than perfect.[9] The CO_2-invariance of SBE versus BE supports the extracellular space as the notional CO_2 equilibration compartment, at least from a modelling perspective. 'Rules-of-thumb,' derived from a meta-analysis of published numerical and graphical data, were eventually developed by the late Robert Schlichtig to describe the expected SBE responses in acute and chronic acid-base disturbances.[10]

With the trans-Atlantic stand-off thus established,[11] enter the Canadian, Peter Stewart, Professor of Medical Science at Brown University, Rhode Island. Professor Stewart was an original thinker and enthusiastic teacher, but he published surprisingly little on the subject of acid-base - one small book[12] and two journal articles.[13,14] His concepts were thus slow to receive world attention. When he died in 1993, 12 years after the book was published, he would have had just an inkling of its eventual impact.

Stewart's 'Heresy'

His was a reductionist approach, essentially a reframing of long-established physical chemical concepts. Continued poor acceptance by both Copenhagen[8] and Boston schools[15] can be attributed to one 'heretical' assertion - that in body fluids, pH and $[HCO_3^-]$ are dependent variables, which cannot be manipulated directly.

Putting Stewart in Context

There is a tendency to regard the Stewart approach as an esoteric system of analysis, embraced by a small group of fanatics who reject all standard approaches. The reality is different. For most of its supporters, Stewart's contribution neither invalidates nor supplants the traditional systems,[16-18] but provides insights into their physiologic basis, and extends their utility.[19] For example, Stewart's concepts provide an accessible, logical framework to progress the author's area of research, which deals with the influence of resuscitation fluid design on acid-base balance.[20-25]

The All-Important $PaCO_2$/pH Relationship

Stewart was able to cast light on the complex interaction between $PaCO_2$ and pH, a relationship fundamental to the methodology of either traditional school. $PaCO_2$ and pH are the only directly measured acid-base variables in a standard blood gas printout. Together they form the clinician's 'diagnostic window', the basis of the acid-base 'primary survey'.[26] Simultaneous values combine to generate the derived metabolic acid-base variables, $[HCO_3^-]$ (Boston) and SBE (Copenhagen).

To illustrate this relationship, it is instructive to consider a scenario in which a group of paralysed, sedated, mechanically-ventilated individuals with stable CO_2 production is subjected

Table. Two sets of arterial blood gas results, two hours apart, in a patient with severe type 2 respiratory failure and fluctuating $PaCO_2$ levels.

	Initial	After 2 hours
pH	7.16	7.30
$PaCO_2$ (mm Hg)	172	124
$[HCO_3^-]$ (mmol/L)	59	59
BE (mEq/L)	19.1	23.5
SBE (mEq/L)	29.1	30.7

to stepwise minute ventilation adjustments, alternately increasing and decreasing, over a few hours. The aim would be to generate a range of equilibrium $PaCO_2$ and pH values prior to the influence of renal compensation. At each step, arterial blood gas analysis would show that:

1. In any individual, a given $PaCO_2$ generates a particular arterial pH.
2. In any individual, each change in $PaCO_2$ moves arterial pH along a characteristic in vivo 'CO_2 titration curve' (Figure 1).
3. The position and shape of this curve varies slightly from individual-to-individual in health, but major shifts occur in metabolic acid-base disturbances, either primary or compensatory (Figure 1).
4. Although $PaCO_2$ and pH are related at every step via the Henderson-Hasselbalch equation (vide infra), this relationship is insufficient on its own to predict the arterial pH at the next $PaCO_2$.

In fact the Henderson-Hasselbalch equation is just one of several determinants of the shape and position of the $PaCO_2$/pH curve, a fact often overlooked by advocates of bicarbonate-based approaches. Peter Stewart gave us (nearly) all of the rest.

In a nutshell, Stewart reminded us that the pH of any body fluid is a function of water dissociation modified by PCO_2, other weak acids and certain electrolytes. He identified several simultaneous equilibria operating under the constraints of the Laws of Mass Action, Mass Conservation, and Electrical Neutrality. On this basis, Stewart set out six equations which can be used to define the PCO_2/pH relationship. As we shall see, they really describe this relationship in separated plasma, falling short of the mark with true plasma, either invitro or in vivo.

Equation 1. Water Dissociation

At the core is water dissociation. Since mammals are approximately 60% water, it follows that the behaviour of water is fundamental to acid-base physiology. In its simplest terms, water dissociation can be modelled as follows:

$$H_2O \leftrightarrow H^+ + OH^-$$

By the Law of Mass Action, at equilibrium $[H^+]\,[OH^-] = Kw\,[H_2O]$, where Kw is the temperature-dependent dissociation constant. H_2O is a vast proton reservoir, with a concentration several orders of magnitude greater than that of its two dissociation products (55.5 mol/L versus 160 nmol/L at 37 °C). Consequently, even small dissociation changes, for example, with temperature, can have marked effects on pH.

Because of its numeric predominance, $[H_2O]$ can be combined with Kw to form a composite constant, Kw. The equilibrium equation then simplifies to:

$$[H^+]\,[OH^-] = Kw' \qquad \text{Equation 1}$$

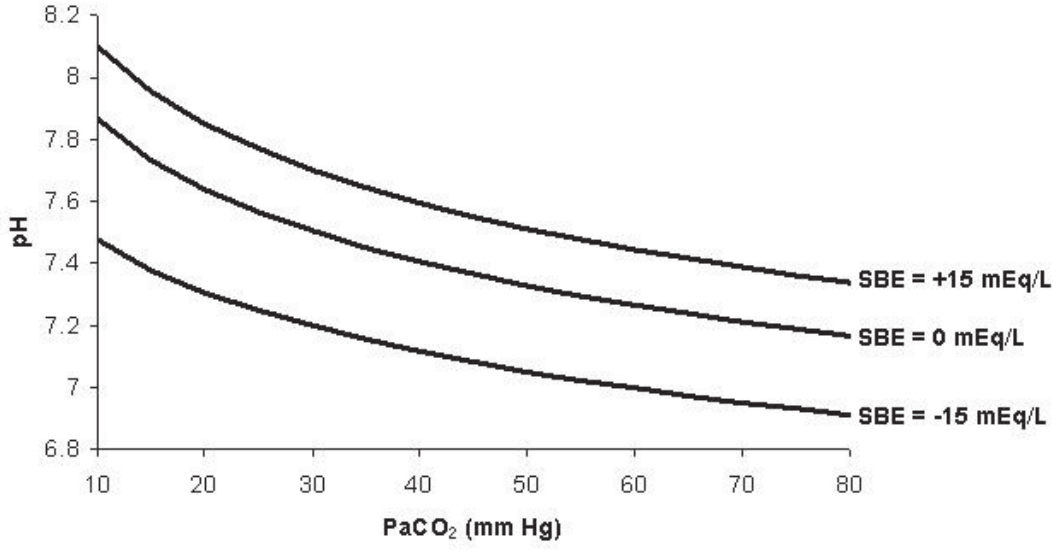

Figure 1. Acute $PaCO_2$/pH curves and associated SBE values (see text). The middle curve (SBE = 0 mEq/L) is normal. Metabolic acidosis (primary or compensatory) causes a down-shift, with SBE increasingly negative. Metabolic alkalosis (primary or compensatory) shifts the curve up, with SBE increasingly positive.

Equation 2. CO_2 and Water

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

By applying the Law of Mass Action and substituting [dissolved CO_2] for [H_2CO_3], the following expression can be derived:

$pH = 6.1 + \log_{10} ([HCO_3^-]/\alpha PCO_2)$ Equation 2

This is the familiar Henderson-Hasselbalch equation, where α is the plasma CO_2 solubility coefficient (0.0301), and 6.1 is the negative logarithm of a dissociation constant modified for [dissolved CO_2].[27]

Equation 3. HCO_3^- Dissociation

This is included for completeness, since HCO_3^- dissociation generates miniscule (micromolar) concentrations of carbonate (CO_3^{2-}) across the physiological pH range:

$[H^+] [CO_3^{2-}] = Kc [HCO_3^-]$ Equation 3

Equation 4. Non-Volatile Weak Acid Dissociation

Fluid compartments have varying concentrations of these non-CO_2 generating (non-volatile) weak acid molecules. Their weak acid properties stem from a negative net molecular charge which alters with pH. In plasma, they consist mainly of albumin and to a lesser extent inorganic phosphate. In red cells haemoglobin predominates. Interstitial fluid contains much smaller non-volatile weak acid concentrations, primarily phosphate.

For convenience, Stewart modelled all non-volatile weak acids in each compartment as having a single anionic form (A^-) and a single conjugate base form (HA).

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

By applying the Law of Mass Action:

$[H^+] [A^-] = K_A [HA]$ Equation 4

Equation 5. Mass Conservation

Stewart termed the total concentration of non-volatile weak acids in any compartment 'A_{TOT}'.

$A_{TOT} = [HA] + [A^-]$ Equation 5

He emphasised that A_{TOT} is an imposed mass constant. It does not vary with pH. A change in pH merely signals a shift in the balance between HA and A^-.

Equation 6. Strong Ion Difference (SID) and Electrical Neutrality

SID, Stewart's best known concept, should be considered in the context of electrical neutrality. Certain elements such as Na^+, K^+, Ca^{2+}, Mg^{2+} and Cl^- exist only as fully ionised entities in body fluids. At physiological pH, this applies to anions with pKa values of 4 or less, at least in the quantitative sense. Examples include sulfate, lactate, and beta-hydroxybutyrate. Stewart termed compounds exhibiting this property 'strong ions'.

In body fluids, there is an excess of strong cations. It is this excess which Stewart quantified as the SID. In other words, SID = [strong cations] – [strong anions]. SID is designed for electrical neutrality statements. It is expressed in mEq/L, as with all acid-base calculations involving the Law of Electrical Neutrality. SID calculated from measured strong ions in normal plasma is 42 mEq/L.

Hence, by the Law of Electrical Neutrality:

$SID + [H^+] - [HCO_3^-] - [CO_3^{2-}] - [A^-] - [OH^-] = 0$ Equation 6

Taken together, Equations 1 - 6 are sufficient to define the PCO_2/pH relationship for separated plasma. They can also be combined and expressed as a fourth order polynomial.[12]

First Sticking Point

It can be argued that Equations 4 and 5 are simplistic in their treatment of non-volatile weak acids. More than one molecular species have been lumped together, making a single value of A_{TOT} and the associated single K_A value difficult to accept. Furthermore, despite their polyprotic nature, there has been no attempt to partition protein or phosphate dissociation and charge behaviour.

In the case of human albumin, each molecule contains >200 dissociable groups,[28,29] prominent contributors being aspartate, glutamate, tyrosine, lysine, arginine and histidine. Apart from a dozen histidines, a solitary cysteine, plus the N-amino terminus, the vast majority act as strong ions throughout physiological pH, fully dissociated at all molecular sites. An anionic preponderance generates the net negative charge. The charge alteration with pH is primarily due to imidazole/imidazolium transitions on histidine.

Several investigators addressed these shortcomings with further experimentation and detailed partitioning, generating mathematical models of greater complexity.[28-32] As yet, none has surpassed the original set of equations as descriptors of the PCO_2/pH relationship.[33]

Weak Ions

Weak ions in body fluids include H^+, OH^-, HCO_3^-, CO_3^{2-}, and A^-. They arise from variably dissociating conjugate bases. From Equation 6, their net charge must always equal SID, which sets their electrical 'boundaries'. However, from a purely quantitative standpoint, HCO_3^- and A^-, known historically as the 'buffer base' anions,[34] occupy the entire SID electrical 'space'. The other ions are present in such minute

concentrations, measured in μmol/L, or in the case of protons, nmol/L, that they are quantitatively insignificant (though they may have marked physiological significance). With this in mind, rearranging Equation 6 gives us $SID = [HCO_3^-] + [A^-]$. SID therefore not only dictates the buffer base concentration, it is numerically identical to it.

This fact, coupled with accurate linear expressions for calculating A^- at physiological pH devised by James Figge,[29] allows us to reduce Stewart's equations in separated plasma to three.

$$[A^-] = [Alb] \times (0.123 \times pH - 0.631) + [Pi] \times (0.309 \times pH - 0.469)$$

$$[HCO_3^-] = 0.0301 \times PCO_2 \times 10^{(pH - 6.1)}$$

$$SID = [HCO_3^-] + [A^-]$$

where [Alb] is albumin concentration, expressed in g/L, [Pi] is phosphate concentration, in mmol/L, PCO_2 is in mm Hg. SID calculated this way is the aforementioned 'buffer base' concentration, also known as the 'effective' SID (SIDe). When SID is calculated from measured plasma concentrations of strong ions, it has been termed the 'apparent' SID, (SIDa). Discrepancies between SIDa and SIDe imply the presence of unmeasured ions in plasma (vide infra).

Second Sticking Point - Stewart's Controversial Assertion

The problem for most traditional physiologists comes with Stewart's next logical step, in which he argued that in biological fluids, pH and HCO_3^-, as well as CO_3^{2-}, A^-, and OH^-, are dependent variables. In other words, they are mere passive players, unable to be altered directly. Stewart named three independent variables as the true controlling factors, imposed on, but not directly altered by the system. They are SID, A_{TOT}, and PCO_2.

According to Stewart, the only way pH or the concentrations of the other dependent variables can change is via one or more of the three independent variables. The reason Stewart chose PCO_2 (usually $PaCO_2$) is because it is governed by external regulation (alveolar ventilation). In a closed system, the relevant independent variable becomes CO_{2TOT}, primarily bicarbonate, with contributions from carbamino groups, carbonic acid, carbonate and dissolved CO_2.

Clearly this has major implications, not just in macro-approaches to renal acid-base homeostasis (vide infra). It goes to the heart of many sub-cellular and molecular processes. Included in this list are a host of membrane H^+/base transporters, the mechanism of mitochondrial oxidative phosphorylation itself, and the functioning of ionophores considered to facilitate proton or HCO_3^- transfer along concentrations gradients. The debate in this area is far from over.[15]

SID and A_{TOT} as Determinants of Metabolic Acid-Base Status

It is easy to show using the above equations that at any given PCO_2, a falling SID or a rising A_{TOT} reduces pH (Figures 2

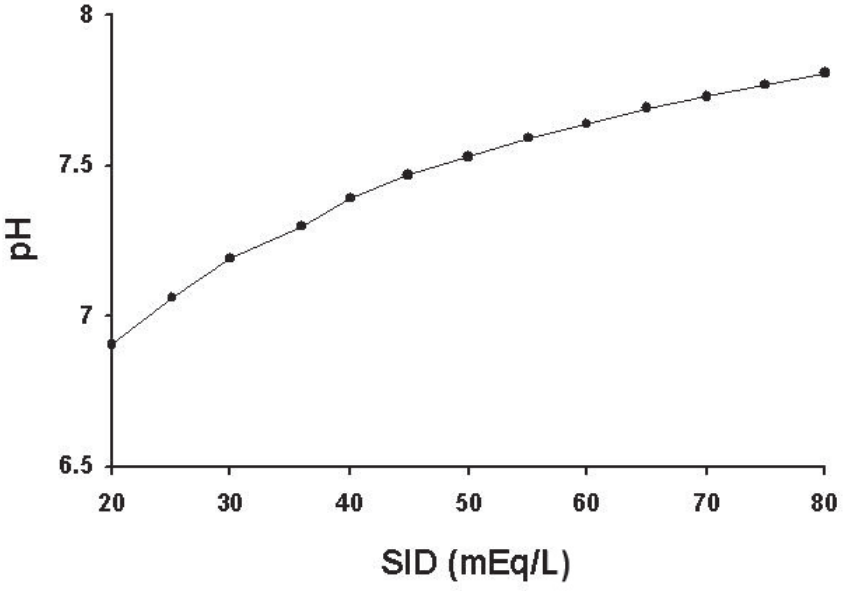

Figure 2. The effect of varying SID on pH in separated plasma. PCO_2 is held constant at 40 mm Hg. A_{TOT} = 20 mEq/L. pK_a = 6.7. SID: strong ion difference, A_{TOT}: Total concentration of non-volatile weak acid.

and 3), moving the equilibrium towards a metabolic acidosis. Conversely, a rising SID or a falling A_{TOT} creates a metabolic alkalosis. This has led Stewart 'purists' to insist that there are four possible metabolic acid-base disturbances, alone, or in combination. Hence, metabolic acidosis can be of the low SID and/or high A_{TOT} varieties. Metabolic alkalosis can fall into high SID and/or low A_{TOT} categories.[35]

Others have noted that SID and A_{TOT} appear to be linked in vivo, with the SID set point adjusting to A_{TOT}. In particular, SID seems to fall in hypoalbuminaemia, presumably by renal chloride adjustment.[36,37]

A Stewart Criticism of the Terms 'Hyperchloraemic' Acidosis and 'Hypochloraemic' Alkalosis

In the Stewart paradigm, plasma [Cl^-] should never be considered in isolation. Its value, together with the concentrations of other strong anions, is relevant only in conjunction with [Na^+], the principal strong cation. The real players determining metabolic acid-base status are SID and A_{TOT}. Consider the following illustrations.

The first comes from 'dilutional' acidosis, a disorder induced by large volume crystalloid and colloid infusions.[38-44] The Stewart approach is an ideal framework for understanding this condition.[24] In saline, both SID and A_{TOT} are zero (equal concentrations of the strong cation Na^+ and the strong anion Cl^-). Rapid infusion simultaneously reduces extracellular SID (metabolic acidosis) and A_{TOT} (metabolic alkalosis) as the infused water and strong ions equilibrate with extracellular fluid. Because SID reduction predominates, metabolic acidosis is the net result.

When isotonic (0.9%) saline is infused in large volumes (for example several litres in a few hours), hyperchloraemia is virtually inevitable and metabolic acidosis highly likely. The point to emphasise, however, is that fluid-induced metabolic acidosis can also result from infusions containing low [Cl^-], such as 0.45% saline, or even zero [Cl^-] such as mannitol.[45] This is because the relevant crystalloid property is not [Cl^-] alone, but the SID. Extracellular SID falls at the same rate in response to any zero SID infusion, whether the fluid being administered has a low, normal or high [Cl^-]. In the case of low [Cl^-] infusions, this will be accompanied by an unchanged or falling extracellular [Cl^-], but always with a greater reduction in [Na^+].

In a second illustration, consider the combination of hypoalbuminaemia and normal plasma [Na^+]. Hyperchloraemia then becomes a prerequisite for a normal overall metabolic acid-base status. In Stewart terms, a reduced SID must counter the low A_{TOT} metabolic alkalosis. Finally, consider metabolic alkalosis and plasma [Cl^-]. Hypochloraemia is unquestionably a common accompaniment. However, with coexistent hypoalbuminaemia, plasma [Cl^-] may be 'normal' or even slightly elevated, especially if the patient is also hypernatraemic.

Hence 'hyperchloraemic' and 'hypochloraemic' are poor acid-base descriptors. Instead of 'hyperchloraemic' metabolic

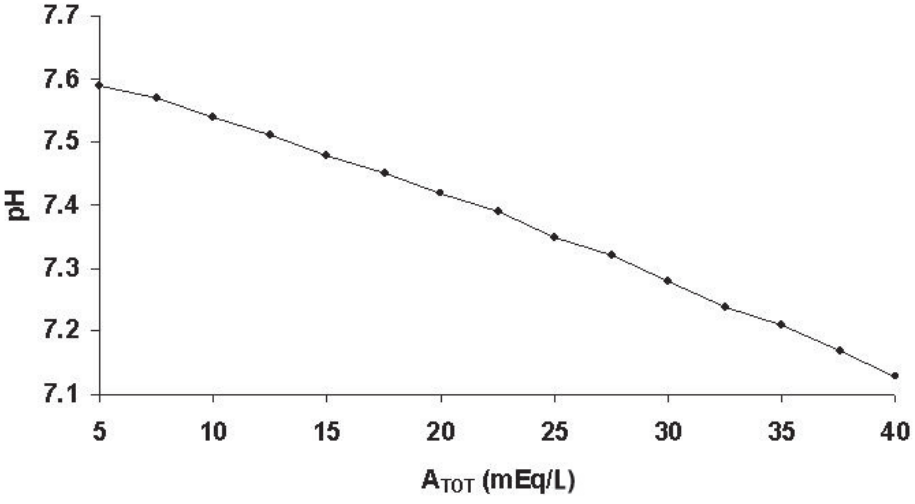

Figure 3. The effect of varying A_{TOT} on pH in separated plasma. PCO_2 is held constant at 40 mm Hg. SID = 42 mEq/L. pK_a = 6.7. SID: strong ion difference, A_{TOT}: Total concentration of non-volatile weak acid.

acidosis, the terms 'normal anion gap,' or 'normal strong ion gap' (vide infra), are better alternatives. More generally, the practice of focusing on [Cl^-] in isolation promotes widespread misunderstanding of both metabolic acidosis and alkalosis.

Third Sticking Point - Separated Plasma versus Real Life

There is one definite flaw in Stewart's original model, similar to the flaw in the BE concept. Separated plasma is not real life. In fact, BE is more 'life-like', since it is modelled on isolated whole blood, a two compartment system. The reality of living organisms is that being multi-compartment systems, they bring the Second Law of Thermodynamics into play. In other words, Stewart's concepts neglect Gibbs-Donnan equilibria and associated trans-membrane ion traffic. (It must be said that Stewart himself dismissed these as having little impact).

Gibbs-Donnan Equilibria

Gibbs-Donnan equilibria operate when a semi-permeable membrane separates fluids, one or both of which contains impermeant ions. Under these conditions, trans-membrane distributions of permeant ions reset to maximise entropy, with electrical gradients balanced against concentration gradients. All fluid compartments are subject to these phenomena, including the intracellular compartment.

Of note, acid-base models incorporating Donnan equilibria seem to retain accuracy if the intracellular compartment is ignored, apart from the erythrocytes (whose intracellular milieu is atypical). Hence, it is enough to consider the interaction between the plasma (compartment volume 3 L, impermeant anion; albumin), the erythrocytes (compartment volume 2 L, impermeant anion; mainly haemoglobin), and the interstitium (compartment volume 13.5 L, impermeant anions; minimal).

Of these, erythrocytes have by far the highest concentrations of trapped negative charges. Therefore their intracellular fluid exerts the most forcible attraction of permeant cations (such as Na^+, K^+) and the strongest repulsion of permeant anions (primarily Cl^-). However, if these forces were to operate unopposed, there would be cell swelling and overwhelming haemolysis. Several cations therefore undergo continual redistribution by energy dependent trans-membrane pumps. Chloride, the major anion, remains largely at the mercy of Donnan effects.

A final factor is differential pH-susceptibility of trapped negative charges, since red cell haemoglobin provides about seven times the buffering capacity of plasma albumin. During pH change, the main participating sites in impermeant molecules on either side of the red cell membrane, are imidazole/imidazoline side chains on histidine, which are either uncharged or, after gaining protons, positively charged. As pH falls, both molecules take on protons at these sites, decreasing their overall negative charge. Because haemoglobin charge alterations exceed those of albumin, there are further immediate trans-membrane ionic redistributions, especially chloride.

The result is perhaps unwelcome news for Stewart 'purists'. Plasma SID is driven up and down in parallel with acute changes in PCO_2.[26] This is a motive force behind the so-called 'Hamburger effect' or 'chloride shift' which accompanies the arterio-venous transition. More importantly from the Stewart perspective, the lack of CO_2-invariance of plasma SID introduces a serious qualification to its 'independent variable' status. However, it appears that CO_2 driven ion shifts are largely contained within the total extracellular space. In other words, total extracellular SID (incorporating the erythrocyte volume) does not alter significantly with acute $PaCO_2$ variations. This underpins the CO_2-invariance of SBE.

Hence, when we graduate from separated plasma to real life, not only Equations 1 to 6, but a number of Gibbs-Donnan equilibria must be satisfied simultaneously. 'Independent variable' status is transferred from plasma to extracellular SID. Arterial plasma pH at any given $PaCO_2$ becomes a complex function of total extracellular SID and A_{TOT}, rather than of the directly measurable plasma SID and A_{TOT}.

A 'Stewart' Insight into SBE

Plasma BE is simply a calculation of the offset in the buffer base concentration of separated plasma.[46] In Stewart terms, plasma buffer base, otherwise known as SIDe, is the quantitative equivalent of plasma SID, as already discussed. Hence, plasma BE expresses the offset in plasma SID. Plasma BE could thus be termed plasma 'SIDex' (the offset in plasma SID). By extension, whole blood BE has already been described as whole blood 'SIDex' (the offset of whole blood SID).[47] Such an extrapolation from separated plasma to whole blood, in other words from a single to a dual compartment system, is more than a leap of faith, since multi-compartment applications of SID theory can be shown to have quantitative equivalence with corresponding Van Slyke equation BE calculations.[48]

So by further extrapolation, this time from whole blood, ex vivo, to the total extracellular compartment (incorporating the erythrocytes), SBE represents the offset in extracellular buffer base. It can therefore be regarded as extracellular 'SIDex'. A typical SBE reference interval (in mEq/L) is –3.0 to +3.0. If SBE = –15.0 mEq/L for example, there is a down-shifted $PaCO_2$/pH curve (Figure 1). This could represent either a

primary metabolic acidosis or else compensation for a primary respiratory alkalosis. From a Stewart perspective, a 15.0 mEq/L increase in extracellular SID corrects the SIDex and returns the curve to its normal mid-position. SBE is therefore roughly the corrective dose of sodium bicarbonate in mmol per litre of extracellular fluid.

Similarly, if SBE >3.0 mEq/L, the curve is displaced upwards, either as a primary metabolic alkalosis or as compensation for a respiratory acidosis. A SBE value of +15 mEq/L means that a 15 mEq/L decrease in extracellular SID is needed to return the curve to its normal position at the prevailing A_{TOT}. Conceptually, it approximates the required dose of HCl per litre of extracellular fluid.

In this way Stewart's concepts shed light on how and why SBE can be used as a clinical therapeutic target.

Renal Participation in Acid-Base - the Physical Chemical Angle

Traditionally, renal acid-base homeostasis has been described in terms of proton excretion coupled with filtered HCO_3^- resorption and new HCO_3^- generation. Proton elimination is facilitated by titration of urinary buffers at low urinary pH, especially the $HPO_4^{2-}/H_2PO_4^-$ system (titratable acidity), and by variable up-regulation of tubular NH_3 excretion to enhance luminal proton 'trapping' as NH_4^+.[49,50]

From the physical chemical perspective, this model is misleading, turning as it does on H^+ or HCO_3^- 'balances'. In the Stewart model, H^+ and HCO_3^- do not answer to 'in versus out' balance sheets. They are dependent variables, passive players responsive exclusively to PCO_2, SID and A_{TOT}.

The physical chemical explanation of renal acid-base homeostasis is simpler, since metabolic acid-base can only be regulated by adjusting extracellular SID and/or A_{TOT}. With the kidneys, SID adjustment is the main tool. There is a minor influence on A_{TOT} via phosphate excretion, which is a totally different concept from that of 'titratable acidity'.

In the Stewart paradigm, the kidneys regulate extracellular SID via urinary SID.[51] For this to be successful there must be an adequate urine output. Tubular NH_4^+ functions as a cationic partner for tubular Cl^- and other urinary strong anions, rather than as a vehicle for removing protons. By substituting for an equal concentration of tubular Na^+, NH_4^+ allows for an 'adjustable' urinary SID.[52] Renal proton 'excretion' is incidental.

It is important to remember that 'urinary SID' is determined by urinary entities that are quantitatively important strong ions in the extracellular fluid environment, not in urine. NH_4^+ can cause confusion on this front.[15] It is a weak (borderline strong) base (pK_a 9.2),[50] present in minute extracellular concentrations outside of the kidney. $[NH_4^+]$ is therefore excluded from the urinary SID calculation, despite its significant urinary concentrations and predominant ionisation at urinary pH.

As an example, consider a dose of HCl (delivered slowly into a central vein). It deposits a negative SID fluid bolus in the intravascular space, which then equilibrates with the remaining extracellular fluid, reducing extracellular SID. The kidneys deal with the resultant metabolic acidosis by boosting urinary $[NH_4^+]$, enabling increased urinary Cl^- loss without accompanying Na^+, the result being a reduction in urinary SID. With sufficient urine output, the prompt fall in urinary SID steadily corrects the extracellular SID.

On the other hand, an intravenous dose of sodium bicarbonate represents a high SID bolus deposited within the extracellular space. Equilibration causes an upswing in extracellular SID, in other words a metabolic alkalosis. Urinary SID undergoes an immediate corrective increase, due to the surge in filtered Na^+, plus suppression of urinary NH_4^+. Although HCO_3^- excretion undoubtedly occurs, it is incidental and secondary.

Renal Failure

In untreated renal failure, there is a progressive metabolic acidosis. Again Stewart gives us a different perspective. About 60 mEq of sulfate, hippurate and other strong anions are produced daily as metabolic end-products. Their retention in renal failure reduces extracellular SID. Free water accumulation brings sodium concentrations closer to chloride, again reducing SID.

Hyperphosphataemia contributes to the acidosis by increasing A_{TOT}, although in acute renal failure this is usually offset by co-existent hypoalbuminaemia, with A_{TOT} reduction overall. Hence, the metabolic acidosis of renal failure is due to a reduction in extracellular SID, sufficient to overwhelm the low A_{TOT} metabolic alkalosis which frequently accompanies acute renal failure.[53]

Renal Tubular Acidosis

The Stewart emphasis in renal tubular acidosis, mechanistically speaking, is on an inappropriately high urinary SID 'setting', and an inadequate urinary SID nadir following an acid load, rather than the inadequately low urinary pH. In Types 1 and 4, the problem is insufficient urinary NH_4^+, and in Type 2 there is excessive proximal resorption of urinary Cl^-.[26]

The Laboratory and the Stewart Approach

SIDa and SIDe

Reporting individual SIDa or SIDe values in isolation may

mislead clinicians. Neither is a reliable measure of metabolic acid-base status, for three reasons:

1. Plasma SID, the only SID available to clinicians, varies with $PaCO_2$, due to Donnan effects. Extracellular SID, an integration of plasma, erythrocyte and interstitial SID, is CO_2-invariant but not directly measurable.
2. SIDa and SIDe can both be inaccurate reflections of the true SID. For example unmeasured strong anions give SIDa positive bias, and unmeasured weak anions, for example infused gelatin,[25] give SIDe negative bias.
3. SID must always be interpreted in conjunction with A_{TOT}, since metabolic acid-base status is a function of the interplay between SID and A_{TOT}. In a healthy individual a plasma SID of 42 mEq/L may be normal, but if there is hypoalbuminaemia (reduced A_{TOT}) it represents a metabolic alkalosis.

'Gaps'

The anion gap is the time-honoured scanning tool for detecting unmeasured anions.[54] It is calculated as $[Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$, although the $[K^+]$ component is optional. Electroneutrality is the underlying principle, and most of the normal anion gap is due to the A^- component of plasma A_{TOT} (the negative charge on albumin and phosphate). It works best in combination with a global index of acid-base status such as SBE.[47]

In reality, the anion gap quantifies [unmeasured anions] - [unmeasured cations], both strong and weak. Its value is thus increased by unmeasured anions, and decreased by unmeasured cations. The clinician's primary interest is in detecting endogenous strong anions such as L-lactate and ketoacids, and several toxic anions of exogenous origin such as formate and glycolate.[55,56] Early detection and intervention can be life saving, hence the need for rapid reliable scanning tools. Many of the specific assays have a significant lag time.

The problem with the anion gap is that its signal for unmeasured strong anions is subject to considerable noise, emanating from A_{TOT} fluctuations in hypoalbuminaemia and hyperalbuminaemia,[35] A^- fluctuations with severe pH disturbances,[57,58] and several other factors.[59-63] All reduce sensitivity and specificity when investigating a metabolic acidosis.[64-66]

Improving on the Anion Gap

Advocates of the Stewart approach have suggested several modifications to the anion gap, all aimed at developing more sensitive and specific scanning tools for unmeasured anions. The tendency is for these newer parameters to become imbued with a negative 'Stewart' connotation. This is unwarranted, since they do not turn on Stewart's controversial dependent/independent variable concepts, and are largely extensions of the Law of Electrical Neutrality.

Unfortunately a confusing terminology has grown around these newer tools. Those of greatest interest are the Strong Ion Gap (SIG) and a close cousin, known as 'net unmeasured ions' (NUI), and we will consider these first.

SIG

The SIG concept was proposed by Jones in 1990,[67] and progressed by others, especially John Kellum.[68] It is calculated as $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [L\text{-lactate}] - [A^-] - [HCO_3^-]$. Ionised magnesium concentrations are often either omitted, or included as an estimate (0.7 x total concentration). Since [L-lactate] is available in most ICUs on point-of-care instruments, it is no longer treated as an unmeasured ion.

The SIG can be thought of as SIDa - SIDe, which, in healthy individuals, in an ideal world, ought to be zero. Unmeasured strong anions would then reveal their presence by increasing SIDa, giving SIG a positive value. In fact, positive bias is relatively common,[69,70] presumably reflecting local technology and analytic reference standards. It is thus unwise to assume a zero midpoint for the SIG reference interval.[71] Of course, bias presents no problem once recognised, but the potential for diagnostic error is otherwise significant.[72] Any laboratory reporting of SIG values must establish the local reference interval, incorporating measurement and population variability.

The name 'strong ion gap' is confusing, since any unmeasured ion, strong or weak, can influence the 'gap'. In fact, the SIG shares a common structure with the anion gap, since it quantifies [unmeasured anions] - [unmeasured cations]. Like the anion gap, unmeasured anions reveal their presence by increasing the SIG. The advantage is that the SIG signal is insulated from variations in A_{TOT}, pH, [L-lactate], $[Ca^{2+}]$ and $[Mg^{2+}]$, all of which influence the anion gap. In the case of pH variability, there is a marked demonstrable improvement.[57]

However, the SIG still shares several susceptibilities with the anion gap. Weak anions such as certain myeloma paraproteins increase the SIG. Lithium, an unmeasured strong cation, reduces the SIG. Unmeasured weak cations, for example, after administration of the weak base tris-hydroxymethyl aminomethane (THAM),[73,74] also reduce the SIG.

Another concern has been the summated imprecision of the extra analytes involved in the SIG calculation.[69] Thus far, however, wider confidence intervals have not been evident, with inter-assay variation reported as less than 1 mEq/L (personal communication, J Kellum, 9 December 2007).

The Prognostic Power of the SIG

There are data, both supportive[75-79] and otherwise,[70,80] of the contention that the SIG is an important mortality predictor in a wide cross-section of critical illnesses, perhaps because hidden ions are reflected in its values. This question is complicated by the fact that some therapeutic manoeuvres, such as certain antibiotics[81] and gelatin-based resuscitation colloids,[25,82] are themselves likely to increase the SIG.

Hence, the SIG shows some promise in early severity assessment and outcome prediction in acute illness. It is a step forward in design compared with the anion gap. Surprisingly, as yet its sensitivity and specificity in the detection of 'unmeasured' anions have not been directly compared with the anion gap.

Net Unmeasured Ions (NUI)

The NUI calculation, developed by the late Peter Lloyd, has a similar structure to the SIG.[83,84] However, there are several differences in detail, based mainly on the work of Constable.[31,32] Both Stewart and Constable model plasma proteins as weak acids (HA) dissociating to H^+ and A^-. However, as with Watson,[30] Constable partitions the protein negative charge into a fixed component, allocated to the SID, and a variable component assigned to A_{TOT}. He also partitions the phosphate charge. The Constable SID is therefore about 4 mEq/L lower than the Stewart SID. Both refinements are incorporated in the NUI calculation.

Figge and colleagues found that plasma protein acid-base behaviour could be modelled accurately using albumin alone.[28] This approach is widely accepted. However, Constable demonstrated better correlation of measured versus predicted pH when total protein was used in the pH calculation, and the NUI follows this practice. The NUI calculation also attributes trivalent behaviour to the divalent ions calcium, magnesium, monohydrogen phosphate, and sulfate - a modification designed to track their observed deviations from 'ideal' behaviour.

The NUI 'readout' is also different. Whereas the SIG follows the anion gap convention in that a positive value means a predominance of unmeasured anions, Lloyd inverted the sign, so that NUI reflects the actual net charge. A negative NUI therefore represents a predominance of unmeasured anions.

Anion Gap Modifications

More straight-forward anion gap 'corrections' exist, none of proven clinical value. All iterations are based on the Law of Electrical Neutrality, but the degree of complexity and requisite input data vary. All but the simplest require local recalibration against a reference population.

Consider the following examples:

Simple Albumin Correction

The simplest takes the following form: [85]

$AGc = AG + 0.25 \times (40 - [\text{Albumin g/L}])$ mEq/L, assuming the mid-reference value for [albumin] is 40 g/L.

This is a rough correction for albumin concentrations only. It ignores the phosphate contribution to A^-, and attributes a fixed negative charge to albumin, making no adjustment for pH effects. The main advantage is that the reference interval for the uncorrected anion gap is normally used. It is unclear whether there is a useful increase in sensitivity.[86]

Simple Albumin and Phosphate Correction

Kellum has suggested subtracting the 'true' AG derived from [albumin] and [phosphate] from the traditionally calculated 'apparent' AG.[52] His model assigns fixed albumin and phosphate negative charges, preset for acidaemic conditions.

$$AGc = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) - (0.2[Alb] + 1.5[Pi])$$

[Alb] is albumin concentration expressed in g/L, [Pi] is phosphate concentration in mmol/L.

In fact, despite the name, this is more a 'rough' SIG calculation, and, as with the SIG, should approximate zero in normals.[19]

More Detailed Albumin and Phosphate Corrections

A more complex version incorporates the Figge determination of plasma $[A^-]$.[29] This brings it closer to the complete SIG calculation, with only $[Ca^{2+}]$, $[Mg^{2+}]$ and [L-lactate] now omitted:

$$AGc = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) - ([Alb] \times (0.123 \times pH - 0.631) + [Pi] \times (0.309 \times pH - 0.469))$$

The BE Gap

The 'BE gap' is an attempt to combine the methodology of Siggaard-Andersen and Stewart by partitioning whole blood BE into four physical chemical segments. This is the so-called 'Fencl Stewart' approach,[87,88] regarded by many (including this author) as contentious, not least because it is invalid to assume that whole blood BE (rather than plasma BE) can be partitioned into plasma segments.

Which to Choose?

There have been other proposed parameters. Unfortunately, an acid-base consensus conference is needed to evaluate each one, in order to produce uniform recommendations on validity, terminology and application. In the meantime, individual

laboratories must make local decisions in consultation with their critical care physicians.

Stewart 'Packages'

Meanwhile composite acid-base reports incorporating the Stewart approach, with in-built decision support, are appearing. Clinical biochemists should be aware of two current developments. They are the Strong Ion Calculator, out of New Zealand, and the website Acidbase.org, based in The Netherlands.

The Strong Ion Calculator - a Laboratory Application of the Stewart Approach

The Strong Ion Calculator is a software program linked to the Laboratory Information System of Hawke's Bay Regional Hospital, Hastings, New Zealand.[83,84] It was developed by the late Peter Lloyd to counter criticism that the Stewart approach lacks bedside utility. The Calculator incorporates the NUI calculation. It also displays the offset in proton activity (in nmol/L) caused by the abnormality in each independent acid-base variable (SID, A_{TOT} and PCO_2), determined at the actual values of the other two (Figure 4). Clinicians should find this both meaningful and practical, although it must be remembered that total extracellular rather than plasma SID and A_{TOT} values are the true independent variables.

Acidbase.org - an Online Resource

A related tool is now available at www.acidbase.org.[89] Here, clinicians can enter patient acid-base and chemistry data online, and obtain online decision support for complex acid-base disorders.[90]

Like the Strong Ion Calculator, Acidbase.org provides a breakdown of the relative contributions to the overall pH disturbance by its major controlling elements - $PaCO_2$ (respiratory component), albumin and phosphate (weak acid component), L-lactate, 'corrected' chloride, and unmeasured ions. The 'corrected' chloride concept is based on the contentious Fencl-Stewart approach,[87,88] where plasma [Cl^-] is adjusted for any free water disturbance (calculated from the offset in plasma [Na^+]). The 'corrected' value is then reported in direct acid-base terms, as normal, hyperchloraemic acidosis or hypochloraemic alkalosis.

As with the Strong Ion Calculator, the pH offset due to each factor is calculated and displayed graphically at the existing values of the others, giving the clinician a 'feel' for the relative severity of each perturbation. An added feature is the opportunity for the clinician to juggle individual factors in virtual scenarios. The potential impact of specific interventions can thus be assessed. There are also built-in educational hot-links.

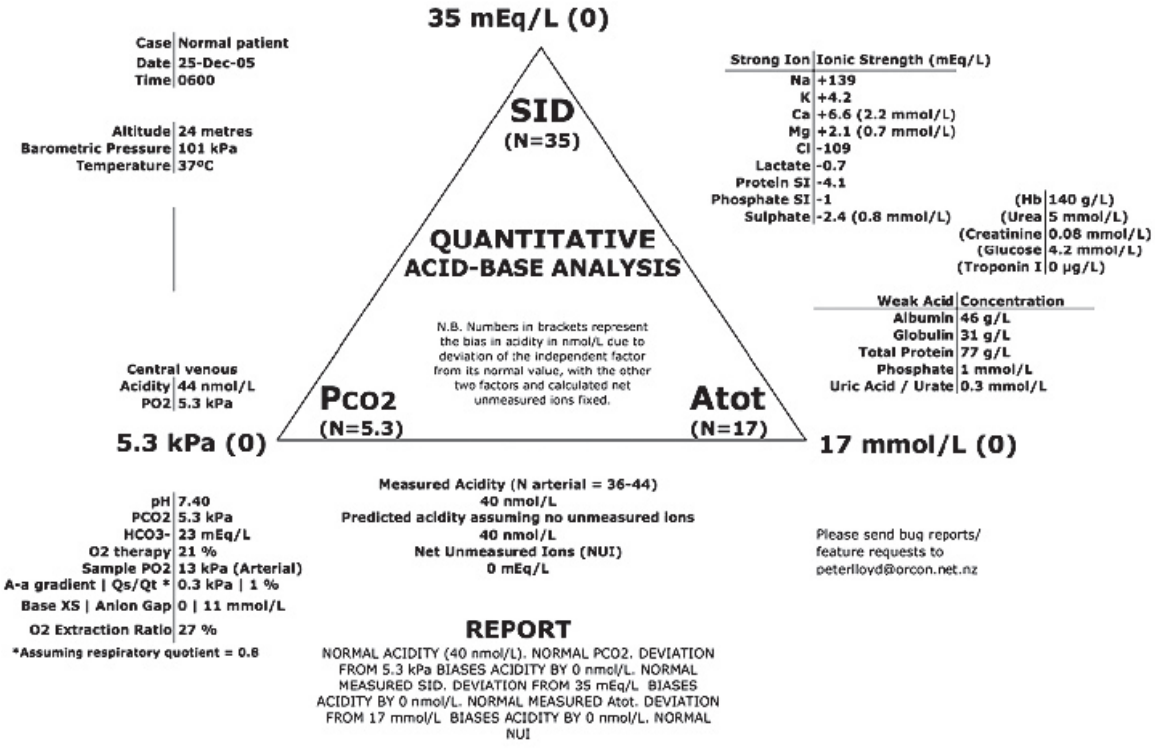

Figure 4. An example of a report from the Strong Ion Calculator from Lloyd P (reference 83). (Permission granted by the Joint Faculty of Intensive Care Medicine).

Although it currently has contentious features, Acidbase.org will continue to evolve. It is likely to become an increasingly valuable resource over time. Perhaps more importantly, it can serve as an acid-base reporting model for laboratory information systems.

Most notably, the original text of Stewart's book is freely accessible at this site. The good news is that a 2009 edition of this landmark publication, entitled 'Stewart's Textbook of Acid-Base', has now been published by Acidbase.org. It contains twenty new chapters. Details can be found on the website.[89]

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References

1. Astrup P, Severinghaus, J.W. The History of Blood gases, Acids and Bases. Copenhagen: Munksgaard; 1986.
2. Siggaard-Andersen O, Engel K, Jorgensen K, Astrup P. A Micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood. Scand J Clin Lab Invest 1960;12: 172-6.
3. Severinghaus JW. Siggaard-Andersen and the "Great Trans-Atlantic Acid-Base Debate". Scand J Clin Lab Invest Suppl 1993;214:99-104.
4. Siggaard-Andersen O. The van Slyke equation. Scand J Clin Lab Invest Suppl 1977;37:15-20.
5. Morgan TJ, Clark C, Endre ZH. Accuracy of base excess--an in vitro evaluation of the Van Slyke equation. Crit Care Med 2000;28:2932-6.
6. Schwartz WB, Relman AS. A critique of the parameters used in the evaluation of acid-base disorders. "Whole-blood buffer base" and "standard bicarbonate" compared with blood pH and plasma bicarbonate concentration. N Engl J Med 1963;268:1382-8.
7. Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. Medicine (Baltimore) 1980;59:161-87.
8. 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;107:123-8.
9. Park M, Maciel AT, Noritomi DT, Pontes de Azevedo LC, Taniguchi LU, da Cruz Neto LM. Effect of $PaCO_2$ variation on standard base excess value in critically ill patients. J Crit Care 2009;in press.
10. Schlichtig R, Grogono AW, Severinghaus JW. Human PaCO2 and standard base excess compensation for acid-base imbalance. Crit Care Med 1998;26:1173-9.
11. Severinghaus JW. Acid-base balance nomogram--a Boston-Copenhagen detente. Anesthesiology 1976;45: 539-41.
12. Stewart PA. How to understand acid-base. A quantitative acid-base primer for biology and medicine. New York: Elsevier; 1981.
13. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444-61.
14. Stewart PA. Independent and dependent variables of acid-base control. Respir Physiol 1978;33:9-26.
15. Kurtz I, Kraut J, Ornekian V, Nguyen MK. Acid-base analysis: a critique of the Stewart and bicarbonate-centered approaches. Am J Physiol Renal Physiol 2008;294:F1009-31.
16. McNamara J, Worthley LI. Acid-base balance: part I. Physiology. Crit Care Resusc 2001;3:181-7.
17. McNamara J, Worthley LI. Acid-base balance: part II. Pathophysiology. Crit Care Resusc 2001;3:188-201.
18. Gluck SL. Acid-base. Lancet 1998;352:474-9.
19. Kellum JA. Clinical review: reunification of acid-base physiology. Crit Care 2005;9:500-7.
20. Morgan TJ, Venkatesh B, Hall J. Crystalloid strong ion difference determines metabolic acid-base change during acute normovolaemic haemodilution. Intensive Care Med 2004;30:1432-7.
21. Morgan TJ, Venkatesh B, Hall J. Crystalloid strong ion difference determines metabolic acid-base change during in vitro hemodilution. Crit Care Med 2002;30:157-60.
22. Morgan TJ, Venkatesh B, Beindorf A, Andrew I, Hall J. Acid-base and bio-energetics during balanced versus unbalanced normovolaemic haemodilution. Anaesth Intensive Care 2007;35:173-9.
23. Morgan TJ, Power G, Venkatesh B, Jones MA. Acid-base effects of a bicarbonate-balanced priming fluid during cardiopulmonary bypass: comparison with Plasma-Lyte 148. A randomised single-blinded study. Anaesth Intensive Care 2008;36:822-9.
24. Morgan TJ. The meaning of acid-base abnormalities in the intensive care unit: part III -- effects of fluid administration. Crit Care 2005;9:204-11.
25. Morgan TJ, Vellaichamy M, Cowley DM, Weier SL, Venkatesh B, Jones MA. Equivalent metabolic acidosis with four colloids and saline on ex vivo haemodilution. Anaesth Intensive Care 2009; in press.
26. Morgan TJ. Acid-base balance and disorders. In: Bersten AD, Soni N, editors. Oh's Intensive Care Manual. 6th ed. Philadelphia: Butterworth-Heinemann Elsevier; 2009. p. 949-961.
27. Lumb AB. Carbon dioxide. In: Nunn's Applied Respiratory Physiology. 6th ed. Philadelphia: Butterworth-Heinemann Elsevier; 2005. p. 148-165.
28. Figge J, Rossing TH, Fencl V. The role of serum proteins in acid-base equilibria. J Lab Clin Med 1991;117:453-67.

29. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. J Lab Clin Med 1992;120: 713-9.
30. Watson PD. Modeling the effects of proteins on pH in plasma. J Appl Physiol 1999;86:1421-7.
31. Staempfli HR, Constable PD. Experimental determination of net protein charge and A(tot) and K(a) of nonvolatile buffers in human plasma. J Appl Physiol 2003;95:620-30.
32. Constable PD. A simplified strong ion model for acid-base equilibria: application to horse plasma. J Appl Physiol 1997;83:297-311.
33. Anstey CM. Comparison of three strong ion models used for quantifying the acid-base status of human plasma with special emphasis on the plasma weak acids. J Appl Physiol 2005;98:2119-25.
34. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine (Baltimore) 1948;27:223-42.
35. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 2000;162:2246-51.
36. Wooten EW. Analytic calculation of physiological acid-base parameters in plasma. J Appl Physiol 1999;86: 326-34.
37. Wilkes P. Hypoproteinemia, strong-ion difference, and acid-base status in critically ill patients. J Appl Physiol 1998;84:1740-8.
38. Waters JH, Miller LR, Clack S, Kim JV. Cause of metabolic acidosis in prolonged surgery. Crit Care Med 1999;27:2142-6.
39. Takil A, Eti Z, Irmak P, Yilmaz Gogus F. Early postoperative respiratory acidosis after large intravascular volume infusion of lactated ringer's solution during major spine surgery. Anesth Analg 2002;95:294-8.
40. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90:1265-70.
41. Rehm M, Orth V, Scheingraber S, Kreimeier U, Brechtelsbauer H, Finsterer U. Acid-base changes caused by 5% albumin versus 6% hydroxyethyl starch solution in patients undergoing acute normovolemic hemodilution: a randomized prospective study. Anesthesiology 2000;93:1174-83.
42. Prough DS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 1999;90: 1247-9.
43. Mustafa I, Leverve XM. Metabolic and hemodynamic effects of hypertonic solutions: sodium lactate versus sodium chloride infusion in postoperative patients. Shock 2002;18:306-10.
44. McFarlane C, Lee A. A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. Anaesthesia 1994;49:779-81.
45. Makoff DL, da Silva JA, Rosenbaum BJ, Levy SE, Maxwell MH. Hypertonic expansion: acid-base and electrolyte changes. Am J Physiol 1970;218:1201-7.
46. Siggaard-Andersen O. Titratable acid or base of body fluids. Ann N Y Acad Sci 1966;133:41-58.
47. Schlichtig R, Grogono AW, Severinghaus JW. Current status of acid-base quantitation in physiology and medicine. Anesthesiol Clin North Am 1998;16:211-33.
48. Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. J Appl Physiol 2003;95:2333-44.
49. Rodriguez-Soriano J. Renal tubular acidosis: the clinical entity. J Am Soc Nephrol 2002;13:2160-70.
50. Guyton AC, Hall JE. Regulation of Acid-Base Balance. In: Textbook of Medical Physiology. 11th ed. Philadelphia: Elsevier Saunders; 2005. p. 383-481.
51. Gattinoni L, Carlesso E, Cadringher P, Caironi P. Strong ion difference in urine: new perspectives in acid-base assessment. Crit Care 2006;10:137.
52. Kellum JA. Determinants of plasma acid-base balance. Crit Care Clin 2005;21:329-46.
53. Rocktaschel J, Morimatsu H, Uchino S, Ronco C, Bellomo R. Impact of continuous veno-venous hemofiltration on acid-base balance. Int J Artif Organs 2003;26:19-25.
54. Emmett M, Narins RG. Clinical use of the anion gap. Medicine (Baltimore) 1977;56:38-54.
55. Peterson CD, Collins AJ, Himes JM, Bullock ML, Keane WF. Ethylene glycol poisoning: pharmacokinetics during therapy with ethanol and hemodialysis. N Engl J Med 1981;304:21-3.
56. Gonda A, Gault H, Churchill D, Hollomby D. Hemodialysis for methanol intoxication. Am J Med 1978;64:749-58.
57. Morgan TJ, Cowley DM, Weier SL, Venkatesh B. Stability of the strong ion gap versus the anion gap over extremes of PCO2 and pH. Anaesth Intensive Care 2007;35:370-3.
58. Madias NE, Ayus JC, Adrogue HJ. Increased anion gap in metabolic alkalosis: the role of plasma-protein equivalency. N Engl J Med 1979;300:1421-3.
59. Oster JR, Gutierrez R, Schlessinger FB, Taylor A, Federman DG, Vaamonde CA. Effect of hypercalcemia on the anion gap. Nephron 1990;55:164-9.
60. Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol 2008;3:208-25.
61. Kelleher SP, Raciti A, Arbeit LA. Reduced or absent

serum anion gap as a marker of severe lithium carbonate intoxication. Arch Intern Med 1986;146:1839-40.

62. Goldstein RJ, Lichtenstein NS, Souder D. The myth of the low anion gap. JAMA 1980;243:1737-8.
63. Clark BA, Brown RS. Unsuspected morbid hypermagnesemia in elderly patients. Am J Nephrol 1992;12:336-43.
64. Salem MM, Rosa RM, Batlle DC. Extrarenal potassium tolerance in chronic renal failure: implications for the treatment of acute hyperkalemia. Am J Kidney Dis 1991;18:421-40.
65. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP. Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. Crit Care Med 1990;18:275-7.
66. Adams BD, Bonzani TA, Hunter CJ. The anion gap does not accurately screen for lactic acidosis in emergency department patients. Emerg Med J 2006;23:179-82.
67. Jones NL. A quantitative physicochemical approach to acid-base physiology. Clin Biochem 1990;23:189-95.
68. Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care 1995;10:51-5.
69. Story DA, Poustie S, Bellomo R. Comparison of three methods to estimate plasma bicarbonate in critically ill patients: Henderson-Hasselbalch, enzymatic, and strong-ion-gap. Anaesth Intensive Care 2001;29: 585-90.
70. Cusack RJ, Rhodes A, Lochhead P, Jordan B, Perry S, Ball JA, et al. The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. Intensive Care Med 2002;28:864-9.
71. Martin M, Murray J, Berne T, Demetriades D, Belzberg H. Diagnosis of acid-base derangements and mortality prediction in the trauma intensive care unit: the physicochemical approach. J Trauma 2005;58: 238-43.
72. Morimatsu H, Rocktaschel J, Bellomo R, Uchino S, Goldsmith D, Gutteridge G. Comparison of point-of-care versus central laboratory measurement of electrolyte concentrations on calculations of the anion gap and the strong ion difference. Anesthesiology 2003;98: 1077-84.
73. Hoste EA, Colpaert K, Vanholder RC, Lameire NH, De Waele JJ, Blot SI, et al. Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. J Nephrol 2005;18:303-7.
74. Holmdahl MH, Wiklund L, Wetterberg T, Streat S, Wahlander S, Sutin K, et al. The place of THAM in the management of acidemia in clinical practice. Acta Anaesthesiol Scand 2000;44:524-7.
75. Murray D, Grant D, Murali N, Butt W. Unmeasured anions in children after cardiac surgery. J Thorac Cardiovasc Surg 2007;133:235-40.
76. Kaplan LJ, Kellum JA. Comparison of acid-base models for prediction of hospital mortality after trauma. Shock 2008;29:662-6.
77. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med 2004;32:1120-4.
78. Durward A, Tibby SM, Skellett S, Austin C, Anderson D, Murdoch IA. The strong ion gap predicts mortality in children following cardiopulmonary bypass surgery. Pediatr Crit Care Med 2005;6:281-5.
79. Dondorp AM, Chau TT, Phu NH, Mai NT, Loc PP, Chuong LV, et al. Unidentified acids of strong prognostic significance in severe malaria. Crit Care Med 2004;32:1683-8.
80. Rocktaeschel J, Morimatsu H, Uchino S, Bellomo R. Unmeasured anions in critically ill patients: can they predict mortality? Crit Care Med 2003;31:2131-6.
81. Lipner HI, Ruzany F, Dasgupta M, Lief PD, Bank N. The behaviour of carbenicillin as a nonreabsorbable anion. J Lab Clin Med 1975;86:183-94.
82. Hayhoe M, Bellomo R, Liu G, McNicol L, Buxton B. The aetiology and pathogenesis of cardiopulmonary bypass-associated metabolic acidosis using polygeline pump prime. Intensive Care Med 1999;25:680-5.
83. Lloyd P, Freebairn R. Using quantitative acid-base analysis in the ICU. Crit Care Resusc 2006;8:19-30.
84. Lloyd P. Strong ion calculator--a practical bedside application of modern quantitative acid-base physiology. Crit Care Resusc 2004;6:285-94.
85. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. Crit Care Med 1998;26:1807-10.
86. Dinh CH, Ng R, Grandinetti A, Joffe A, Chow DC. Correcting the anion gap for hypoalbuminaemia does not improve detection of hyperlactataemia. Emerg Med J 2006;23:627-9.
87. Gilfix BM, Bique M, Magder S. A physical chemical approach to the analysis of acid-base balance in the clinical setting. J Crit Care 1993;8:187-97.
88. Boyle M, Lawrence J. An easy method of mentally estimating the metabolic component of acid/base balance using the Fencl-Stewart approach. Anaesth Intensive Care 2003;31:538-47.
89. Acidbase.org. http://www.acidbase.org (Accessed 15 January 2009).
90. Elbers PW, Gatz R. Acidbase.org: online decision support for complex acid-base disorders using the Stewart approach. Anesthesiology 2008;109:A1436.