Editorials

"Shh! I think it's the patient"

"But the patient is intubated and unconsciousness, communication is impossible".

Is it? Sedation regimens are often tailored to facilitate SIMV and pressure support modes and while interaction may be limited in the mechanically ventilated patient, they are often able to see, feel and hear – a reassuring smile, touch or sound from a clinician who cares. The emotional condition of a patient is still as basic as any single factor in the treatment of disease and is certainly no less so when technology abounds.

A letter from Sally Magnusson (page 217 of this issue) which was first published in *The Herald* (Glasgow) tells of a sad outpatient experience. Sad because it is believable that a similar story could be told from a friend or relative of any subspecialty patient.

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Finding common ground in acid-base

In this issue of *Critical Care and Resuscitation*, two articles address the concept of strong ion difference (SID), in particular as it relates to dilutional metabolic acidosis.[1,2] This is timely. Critical care practitioners need to come to grips with the physical-chemical approach to acid-base, which is being hailed as a breakthrough by some of our colleagues. In order to place this relative newcomer into context, it is necessary to review events leading up to its emergence.

Acid base physiology and the interpretation of blood gases have been dogged by controversy for many years. Although most practitioners have agreed to use plasma pH (rather than $[H^+]$) as the overall measure of acid-base balance and blood PCO_2 as the sole index of respiratory acid-base status, no single method of quantifying the 'non-respiratory' or metabolic component of acid-base balance has ever met with universal acceptance.

The debate started in earnest in the 60's after Siggaard-Andersen and Engel proposed the parameter 'base excess' (BE) as a CO_2-invariant measure of the metabolic acid-base status of the blood,[3] following on from the related concepts of 'buffer base'[4] and 'standard bicarbonate'.[5] Whole blood BE was defined as zero when pH = 7.4 and PCO_2 = 40 mmHg (both measurements at 37°C). If pH ≠ 7.40 or PCO_2 ≠ 40 mmHg, BE was defined as the concentration of titratable hydrogen ion required to return the pH to 7.4 after PCO_2 is first returned to 40 mmHg. BE was calculated from plasma pH, blood PCO_2 and haemoglobin concentration, initially using an experimentally determined nomogram and subsequently from the purely theoretical Van Slyke equation.[6]

It was soon reported by other workers that BE is inaccurate when used to quantify *in vivo* blood metabolic acid-base change.[7] This is because BE is an *in vitro* measure of blood metabolic acid-base balance, whereas buffering *in vivo* occurs throughout the entire extracellular fluid compartment. Specifically, an *in vivo* change in blood PCO_2 causes BE to change in the opposite direction (despite the fact that no metabolic acid-base change has occurred) due to transfer of bicarbonate and other ions between the intravascular compartment and the less well-buffered interstitial compartment.

Consequently the Boston 'school' promoted six new equations derived from *in vivo* data, in opposition to BE.[8] These equations were claimed to be a better description of the relationships between pH, PCO_2 and bicarbonate *in vivo* during respiratory and metabolic acid-base disturbances. Practitioners using the Boston method were encouraged to memorise these equations in order to interpret blood gas results at the bedside. The advocates of BE responded by calculating BE at a haemoglobin concentration of approximately 50 g/L in order to replicate the mean extracellular haemoglobin concentration. The BE value calculated in this way was termed standard BE (SBE). Similar 'rules of thumb' equations derived by meta-analysis of published numerical and graphical data now describe the appropriate SBE responses in acute and chronic acid-base disturbances.[9] According to this meta-analysis, SBE *in vivo* does not change during acute alterations of PCO_2 (this would be untrue in severe hypocapnia causing a concurrent lactic acidosis[10]), which supports the contention that the extracellular space is the appropriate buffering compartment.

An uneasy truce was established between the Boston and Copenhagen schools, but practitioners from both camps continued to disagree despite attempts at *détente.*[11,12] Conditions were ripe for the arrival of a new challenger. This came in the form of the Stewart physical-chemical approach.[13] The basis of the Stewart

analysis is that [HCO_3^-] and pH can be regarded as dependent variables determined by the independent variables PCO_2, the total concentration of weak acid ([A_{TOT}]), and SID. Strong ions are defined as ions which remain almost completely ionised throughout the physiological pH range (e.g. Na^+, K^+, Cl^-, lactate). There is normally a surfeit of strong cations of approximately 40 mEq/L. To preserve electrical neutrality, this gap is filled passively by HCO_3^- and the anions of weak acids (A^-). The most important weak acid in plasma is albumin (and in whole blood it is haemoglobin). Using these principles, sets of simultaneous equations can be solved such that if any three of pH, PCO_2, [A_{TOT}], and SID are known, the other parameter can be calculated.[14]

Although the Stewart approach first came to light in the early 80's, it took time to receive a lot of attention. It is now being hailed by some as "revolutionary",[15] and its impact on acid-base analysis has even been likened to the impact of Copernicus on earth-centred astronomy.[16] The response of the Copenhagen school to this challenge was also slow in coming but ultimately vigorous,[17] and the acid-base debate was reopened on a new front. Fortunately, the intervention of Schlichtig, Grogono and Severinghaus should be sufficient to prevent a repetition of the titanic struggles of previous decades.[18] Their analysis makes for rewarding reading, since they show quite clearly that all three schools (Copenhagen, Boston and Stewart) can be reconciled and are merely descriptions of the same processes from three different vantage points. Important in the reconciliation process is the need to realise that:

1. SID calculated for whole blood is numerically the same as the buffer base parameter developed by Singer and Hastings in the 40's.[4] Siggaard-Andersen had already drawn attention to this fact.[17]
2. In the Stewart approach, SID is calculated for plasma, using albumin as the main contributor to A_{TOT}. In order for whole blood SID to be calculated, haemoglobin becomes the dominant contributor to A_{TOT}.[19]
3. Use of plasma SID rather than whole blood SID without taking into account Gibbs-Donnan distributional effects between compartments in the ECF can lead to misleading concepts such as "hypoproteinaemic alkalosis".[20]
4. BE can be regarded as the change in whole blood SID (SIDex) required to bring the pH to 7.4 after the PCO_2 is corrected to 40 mmHg.

The calculation of both plasma and whole blood SID from PCO_2, pH and [A_{TOT}] is quite feasible using a programmable calculator or computer, and is a useful research and conceptual tool. In metabolic acidosis, SID is reduced and in metabolic alkalosis it is increased. However, the 'normal' SID depends on [A_{TOT}], which makes bedside interpretation difficult, and from this author's perspective, SBE is by far the preferable clinical tool.

This brings us back to the concept of 'dilutional' metabolic acidosis. Most critical care practitioners will not dispute the contention that hyperchloraemic (normal anion gap) acidosis can follow volume resuscitation of patients.[21] In this issue, Dr Storey points out that the phenomenon is explained quite simply using SID theory.[1] Since the SID of normal saline is zero, large volume saline resuscitation will 'dilute' the extracellular space, reducing plasma (and whole blood) SID and causing a metabolic acidosis. Applying this conceptual approach, resuscitation with any fluid which tends to reduce plasma and whole blood SID (e.g. mannitol, half-normal saline, hypertonic saline) will have a similar tendency to cause a metabolic acidosis, the important point being that plasma dilution reduces the gap between the plasma chloride and sodium concentrations irrespective of the final chloride concentration itself. By the same token, resuscitation with Hartmann's solution, which has an intrinsic SID of 29 mEq/L after metabolism of the contained lactate, will have a much lower tendency to reduce SID. There is an even lower tendency with similar fluids such as Plasmalyte, and Dr Storey makes these points. His choice of the term "post infusion acidosis" is perhaps no better than the original "dilutional acidosis", since infusion of Plasmalyte and related fluids is unlikely to produce a post infusion acidosis unless the organic anions lactate, acetate or gluconate cannot be metabolised.

In Dr Worthley's contribution[2] he takes issue with the Stewart assertion that [HCO_3^-] is a dependent variable and refocuses on the traditional central role of the bicarbonate buffer pair (PCO_2 and HCO_3^-) and their regulation by the respiratory and renal systems. There is no doubt that long term regulation of [HCO_3^-] occurs as a result of renal action. The question is whether the organism 'sees' HCO_3^- as an entity to be regulated directly or whether regulation of ions such as Na^+ and Cl^- determines the 'space' available for both HCO_3^- and A^-. This is open to some argument,[22] particularly since the complexities of renal acid-base regulation are confusing and at times unclear.[23] SID itself is certainly not subject to direct regulation by any acid-base homeostatic loop. Na^+ is the principal strong cation in SID and its concentration is linked primarily to the preservation of extracellular tonicity. Similarly, neither albumin (A_{TOT} plasma) nor haemoglobin concentrations (A_{TOT} whole blood) are directly linked to acid-base feedback loops. The Cl^- ion is the only component of the SID - A_{TOT} partnership present in sufficient quantities to impact on acid-base balance which also has major links with acid-base homeostatic loops.[24]

Proponents of the Stewart approach attribute renal tubular acidosis to a primary failure of renal Cl^- regulation rather than renal HCO_3^- loss. [25] However, it is a matter of semantics to argue that the fall in plasma $[Cl^-]$ in chronic respiratory acidosis occurs in the context of $[Cl^-]$ acting as an independent variable when the real independent motivating force is a hypercapnic fall in pH.

Finally, it is important to emphasise that changes in BE (or SID and A_{TOT}) really only quantify changes in the PCO_2 / pH (or PCO_2 / HCO_3^-) buffer relationship. Dr Worthley makes a similar point. Such changes tell us very little about whether the underlying process is intrinsically acidifying. As an example it is instructive to expand on Dr Worthley's analogy. If normal saline is used to dilute blood by anaerobic admixture *in vitro*, the BE (or SID) will fall as will the PCO_2. However, the pH will scarcely alter, provided haemoglobin-oxygen saturation is unchanged. Practitioners with access to a blood gas analyser are invited to test this for themselves. However if lactic acid or HCl is added anaerobically to blood *in vitro* to cause the same fall in BE (or SID) as saline dilution, pH will fall dramatically due to a major elevation in PCO_2.[26] The clinical correlation of this simple *in vitro* comparison is that a dilutional acidosis is not intrinsically acidifying, but merely changes the PCO_2/pH buffer relationship. By contrast, the development of lactic acidosis due to widespread discharge by ischaemic tissue of lactate and protons into post-capillary blood changes the PCO_2/pH buffer relationship and is grossly acidifying as well. The two processes are indistinguishable by their effects on SID or BE. Arterial pH will be the same in both processes if CO_2 homeostasis is preserved. This is one reason why extra information is gained by monitoring the veno-arterial PCO_2 gap post cardiac arrest,[27] or the mucosal-arterial PCO_2 gap in covert splanchnic ischaemia.[28]

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Australasian multi-centre clinical trials: design and sample size

In Australasia there is currently a great deal of interest in multi-centre clinical trials. This follows the recent publications from the Canadian Clinical Trials Group,[1] and most recently the announcement from the US National Institutes of Health that a multi-centre trial of low tidal volume therapy in ARDS had found a clear and definitive result.[2] The Australian Clinical Trials Group (CTG) is flourishing and is enthusiastically planning new projects; one of which is a large albumin trial. To maintain and focus this early enthusiasm it is important that these projects are designed with realistic and practical limitations in mind.

First it should be recalled that the Canadian Group commenced operations 10 years ago, and took many years to reach its present standard of excellence. This group was also founded by Critical Care scientists with extensive experience in clinical and basic research and trial design. Next it should be noted that the most successful randomised trials undertaken to date in Critical Care have involved 800 patients (NIH ARDS[2]) and 838 patients (Canadian transfusion requirements study[1]). For us, with our limited resources, to undertake a study with numbers greater than these would most likely cause us to hit major logistic hurdles.

To counter some of these problems there are a number of trial design guidelines that might be useful to consider.

1. Design a study for which there are going to be a large number of patients and which is interesting enough to justify spending a great deal of time on - regardless of the final result. It would be ideal if both possible trial results (i.e. positive and negative) are of interest.
2. Choose a topic for which our best clinical intuition would suggest a likely positive result. Negative studies can be important but usually require greater numbers and may not maintain the researchers enthusiasm for long enough (i.e. trial fatigue).
3. Resist the temptation not to do a pilot study first. Published incidences from overseas sources (usually from the United States of America) are never the same as up to date Australian ones, and without these data, an accurate calculation of the sample size needed is impossible.
   Embarking on a study that has no chance of reaching the numbers needed for a definitive result is the risk one takes if these calculations are inaccurate. Large funding bodies like the NHMRC are talented at spotting such inconsistencies.
4. While it is tempting to design a study that includes many questions, the only reliable way to get a clear conclusion is to ask one question only. The sample size analysis should be based on that question. Multiple arms might be appealing but risk delivering a non-result through inadequate sample size. Make the question a simple, clear and clinically important one.
5. Both arms of the study must include an acceptable therapy to all Intensivists working in the various Units. If one arm is not acceptable, there will be trouble in obtaining either an institutional ethics committee approval or study compliance with some of our colleagues. For example, I don't think that one can design a study which involves no albumin for half the patients unless all Intensivists involved in the study believe that management of patients with (or without albumin) is equally as good. If there is a significant disagreement among the Intensivists involved in the study, concerning the value of albumin, these Intensivists are likely to withdraw their patients from the study. Planned patient numbers will become unachievable.
6. There may be specific patient subgroups where many would consider one arm of therapy (e.g. no albumin in severe burns patients) to be unacceptable. These should be excluded up front.
7. Determine the number of patients that a research nurse in one institution can realistically handle. Perhaps 100-200 per year (at about $50 000 per nurse) is likely to be the maximum for each large institution. Ten large Intensive Care Units could then enrol about 1500 patients per year - if consent was not required and there were no dropouts. A 10,000 patient study would then take 7 years.

   However, 1500 patients seems to me to greatly exceed realistic enrolments (the Australian CTG dopamine study enrolled 300 patients from 6 active units over more than 3 years). A study involving 10 Intensive Care Units would cost $500 000 for each year. The only multicentre clinical study in Intensive

Care or Anaesthesia in Australia to be funded in total to anywhere near this level by the NHMRC has been the epidural 'Master' study. It's a large ask.

8. Design a no consent study if possible, to avoid losing many recruitable patients through lack of consent. Guidelines for these which I have found successful in the past are: both arms must be acceptable clinical practice, both arms must be demonstrably safe, the primary study question must be important and might improve future patients outcomes. Patients must be unable to consent (e.g. are unconscious) and must have the right to withdraw later if they awake and chose to do so, or if their next of kin expresses discontent. If a similar study has been successfully run on a no consent basis in the past (e.g. pre-hospital hypertonic saline in North American trauma patients), this will help the proposed study's credibility.
9. Understand that centers may not commit all the patients in their Intensive Care Unit to a big study over many years, as they may want to do other studies in the same patients during this time. Each patient must be in one study at a time only. To break this rule renders everything invalid.
10. Be wary of conclusions from meta-analyses.[3] Many different results are possible depending on the expertise and honesty of the authors, and on the deficiencies inherent in the primary studies. The Cochrane collaboration meta-analysis found that colloids were associated with increased mortality compared with crystalloids.[4] Soon after, another meta-analysis on the same question from a group with high reputation and integrity found no such association.[5] In my view, meta-analyses, at best, provide a focussed question for a well designed prospective trial.
11. Do not include patient groups with vastly different outcomes unless they are randomised separately by stratification. An imbalance in coronary artery bypass graft patients (with a mortality around 1%) compared with general Intensive Care Unit patients (with a mortality around 15 %) may confound the randomisation and render interpretation of all results unreliable.
12. Sample size calculations are critical. Everything fails if they are not correct. Have them double-checked by an independent group of experts before starting the study. In relation to a definitive colloid/ crystalloid study, Choi *et al*,[5] report that 9107 patients are required to identify a 10% difference in outcome from patients with a baseline mortality of 10%. It may be possible to identify an absolute change in mortality of 3% from a baseline mortality of 10% with 4500 patients.

    It would seem sensible to define a patient group with a higher baseline mortality (20% - 40%) in which fewer numbers (ideally about 1000) would be required.

The Australian multicentre clinical trials group has an exciting future. There will ideally now be a rapid evolution through the present phase of unbridled enthusiasm to the next phase – scientific excellence and well designed successes.

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Hypertonic saline for initial resuscitation? I'd like to see that!

Life originated from the sea at a time when the saline concentration was similar to that of our extracellular fluid. Today the sea has a concentration at least three times that of the human extracellular fluid, and perhaps there are human disorders that require us to return to the healing balm of mother nature's brine.

Hypertonic saline (HTS) has been used for many disorders. To rapidly correct symptomatic acute hyponatraemia,[1] resuscitation for burns victims,[2] osmotherapy for cerebral oedema,[3] an expectorant,[4] and to treat hydatid cysts.[5] Cooper, in this issue of the Journal

presents a case for its use in the pre-hospital resuscitation of hypotensive and head injured trauma patients and describes its use in an ongoing prospective, randomised, controlled, and multicentred study.[6]

The pre-hospital management of the trauma patient has undergone a change over the last decade. Previously 'stabilization' at the scene was recommended to allow airway control and intravenous fluid administration to treat hypovolaemia and hypotension before mobilisation.[7] However, following the report of a reduction in mortality in patients with penetrating torso injuries who were managed with minimal intravenous resuscitation and rapid transport to a trauma centre,[8] pre-hospital management of the trauma patient underwent a change. Currently, airway control, pressure on obvious external haemorrhaging wounds and immediate transport to a trauma centre (with limited intravenous resuscitation occurring during transit) is now being recommended, with full resuscitation being delayed until operative control of the haemorrhage is achieved.[7]

However, in the severely hypotensive trauma patient in whom haemostasis will be delayed, initial administration of intravenous fluids will be required, as the vital organs of brain and heart are susceptible to all but the shortest periods of hypoperfusion.[9] Furthermore, in patients with head injury (a common disorder in multiple trauma victims) secondary brain injury is often caused by hypotension, and invariably leads to a poor outcome.

In this regard HTS could reduce secondary brain injury in patients with head injury and hypotension, by shifting fluid from the intracellular compartment to the extracellular (and intravascular) compartment, increasing intravascular volume (and blood pressure) while reducing cerebral oedema, both of which would improve cerebral perfusion. Experimental models of cerebral injury and hypotension have demonstrated lower CSF pressures and increased blood pressure with HTS resuscitation,[10-12] Also, pre-hospital infusion of HTS has been associated with an increase in blood pressure and an increase in survival to hospital discharge compared with predicted survival; an effect which appeared to be better in patients with low baseline Glasgow coma scores.[13] However, as Cooper points out, no study has yet focussed primarily on the outcome of the hypotensive head injured patient treated with HTS.

In relation to the heart (that other vital organ), HTS may have added benefits. For example, in the experimental model, HTS does not alter ischaemic injury associated with myocardial infarction and reperfusion,[14] and early reperfusion with HTS has been reported to reduce myocardial stunning via a Na^{+}/Ca^{+2} exchange mechanism.[15] While some studies have reported a negative inotropic effect with the acute administration of HTS,[16,17] others have reported an increase in cardiac output due to a positive inotropic effect, peripheral vasodilation and increase in preload.[18,19]

However, there are caveats. The pre-hospital maneuver of infusing HTS in the head injured hypotensive patient is a 'once only' temporising one, which while it may 'hold' the patient for the period of pre-hospital transport, it does so with an average increase in the serum sodium in adults of 10 mmol/L (i.e. increase in osmolality of 20 mosm/kg).[13] The infusion may increase the risk of a rebound rise in ICP,[20] particularly during in-hospital resuscitation, and could also produce severe hypertonicity in patients who have body weights < 50 kg (e.g. children).

Nevertheless, the morbidity and mortality associated with head injuries is high and any treatment that promises benefits and can be delivered easily in the pre-hospital setting, is worth considering. We look forward to the results of Dr. Cooper's trial with eagerness.

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