# Intravenous Fluid Administration and Controversies in Acid-Base

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**ABSTRACT**

**Objective:** *To present an overview of acidosis following intravenous fluid infusion and to highlight the current controversy in acid-base physiology.*

**Data sources:** *Articles and reviews from peer reviewed journals and books on acid-base physiology and post infusion acidosis.*

**Summary of review:** *Infusion of intravenous fluids can produce an acidosis particularly in the setting of large volume infusion. The explanation of this phenomenon has centred around dilution of plasma bicarbonate. An alternative explanation can be found in the work of Peter Stewart, which highlights the use of strong ion difference in assessing metabolic acidosis. The Stewart approach differs from the traditional Henderson-Hasselbalch approach to acid-base. Further study is required to determine which approach is correct. Solutions containing base anions such as lactate may attenuate such an infusion acidosis. Animal and clinical studies using Hartmann's solution and Plasmalyte 148 support this idea.*

**Conclusions:** *There is controversy regarding mechanisms in acid-base physiology. The clinical significance of post infusion acidosis is unclear, however use of Hartmann's solution may minimize the acidosis.* (**Critical Care and Resuscitation 1999; 1: 151-156**)

**Key words:** Acid-base, strong ion difference, Hartmann's solution, dilutional acidosis

Acidosis following administration of intravenous fluids has been recognized since the 1920s.[1] Much of the ensuing literature has centred on the use of sodium chloride solutions, both isotonic and hypertonic.[2] The phenomenon of acidosis following fluid infusion has been referred to as 'dilutional acidosis'[3] and 'hyperchloraemic acidosis'.[4] For reasons to be explained, neither of these terms is desirable. The term 'post infusion acidosis' will be used in this review.

Over the last few decades, published reports of post infusion acidosis in human patients have been small groups or case reports.[5-7] Mathes *et al*, very recently, reported significant acidaemia following large volume 0.9% saline infusion during major surgery in a single patient.[7]

The report and ensuing correspondence[8-11] illustrate the divergent opinions on the underlying pathophysiology and suggest that the phenomenon is far more common in the perioperative period than the sporadic literature would suggest.

## The Henderson-Hasselbalch approach

Acids dissociate to release hydrogen ions and base anions into solution:

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

Weak acids are acids which are not completely dissociated in solution. That is, they have a smaller dissociation constant (Ka) where $Ka = [H^+]\,[A^-]\,/[HA]$. The pKa is the negative log of the dissociation constant and will therefore be larger than the pKa of strong acids (completely dissociated). The degree of dissociation of a weak acid added to a solution will depend on the surrounding pH, pKa of the acid and the amount of acid added to the solution.

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Following work in 1908 by Henderson, carbonic acid ($H_2CO_3$), a weak acid, has been used as the centrepiece of the assessment of plasma acid base status. Plasma acid base status has been described in terms of the Henderson-Hasselbalch equation:

$$pH = pKa + \log [HCO_3^-] / [CO_2]$$

The pKa of the bicarbonate - carbon dioxide buffer system is the pH at which the carbon dioxide concentration is equal to the bicarbonate concentration. $[HCO_3^-]$ is the plasma bicarbonate concentration. $[CO_2]$ is the plasma carbon dioxide concentration. One area of confusion with this equation is that the true acid of the acid-base pair is carbonic acid. For practical applications, the concentration of carbon dioxide is used instead and the pKa is modified to incorporate the chemical relationships between carbonic acid concentration and carbon dioxide concentration.[12]

The explanation of post infusion acidosis has centred on a reduction of plasma bicarbonate relative to carbon dioxide.[13] The suggested mechanism for this has two stages. First, a dilution of both the bicarbonate and carbon dioxide components of plasma by infused fluid. Subsequently, ongoing carbon dioxide production restores the plasma carbon dioxide concentration whilst, in the short term, the plasma bicarbonate concentration remains lower. Examining the Henderson-Hasselbalch equation, the numerator is reduced whilst the denominator is unchanged thus resulting in a reduction in pH.[13] This effect may be enhanced by preceding blood loss reducing bicarbonate concentration prior to the administration of fluid.[11]

In studies and case reports where saline solutions have been administered, acidosis has been accompanied by hyperchloraemia,[2] thus the term hyperchloraemic metabolic acidosis has been used. Using a nephrectomized dog model, Makoff *et al*,[14] demonstrated that for solutions such as mannitol or saline, which do not contain buffer pairs, the post infusion acidaemia was similar. Whilst the saline group were hyperchloraemic, the mannitol group were *hypo*chloraemic (figure 1). Therefore, the post infusion acidosis may or may not be hyperchloraemic depending on the solution administered. Further, the suggested pathophysiology is quite different from hyperchloraemic metabolic acidoses associated with renal dysfunction. Therefore the term hyperchloraemic acidosis is best avoided in the post infusion setting.

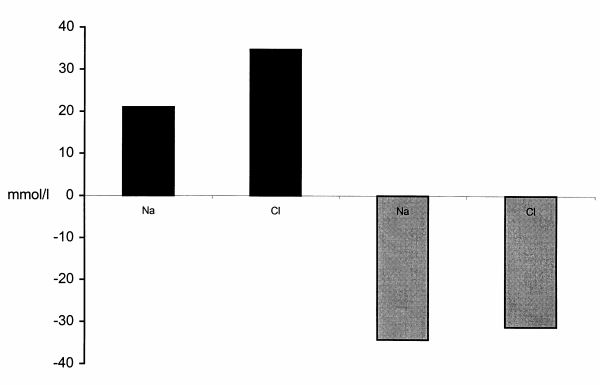


Figure 1. Mean change in sodium and chloride concentrations following administration of 0.75 M NaCl (black columns) and 1.5 M mannitol (grey columns) to nephrectomized dogs (Adapted from Table 1, Makoff et al. Am J Physiol 1970;218:1201-1207)

Some intravenous solutions contain weak acids such as lactic acid, acetic acid and gluconic acid (table 1) which have a pKa of about 3.5. At pH 7.4 these acids are almost entirely in the base anion forms: lactate, acetate and gluconate. The predominant cation in the intravenous solutions and plasma is sodium. One pathway for the elimination of all three weak acids is to be metabolized in the liver to produce bicarbonate.[15,16] It has been proposed that the release of this bicarbonate into the plasma could result in less acidosis following infusion of solutions containing these weak acids.[15]

Traverso and colleagues[17] used a pig model with post hemorrhage resuscitation and found that infusion with acetate and gluconate containing solutions (Plasmalyte, Baxter) and lactate (Hartmann's, Baxter)

**Table 1. Chemical constituents of intravenous fluids in mmol/L**

| | 0.9% saline | Hartmann's | Plasmalyte | Plasmalyte-R | Haemaccel* | Ringers |
|---|---|---|---|---|---|---|
| Sodium | 150 | 129 | 140 | 140 | 150 | 144 |
| Chloride | 150 | 109 | 98 | 103 | 150 | 152 |
| Potassium | 0 | 5 | 5 | 10 | 5.1 | 4 |
| Calcium | 0 | 2.5 | 0 | 5.0 | 6.25 | 2 |
| Magnesium | 0 | 0 | 1.5 | 3 | 0 | 0 |
| Bicarbonate | 0 | 29(lactate) | 27(acetate) 23(gluconate) | 47 (acetate) 8 (lactate) | 0 | 0 |

*Haemaccel also has 35 g/L polygeline.

led to less metabolic acidosis than normal saline. This finding was confirmed clinically by McFarlane and Lee[18] who compared the use of saline and Plasmalyte in general surgical patients and found a postoperative base excess of - 5.0mmol/L in the saline group and - 1.2 mmol/L ($p < 0.01$) in the Plasmalyte group.

At the Austin and Repatriation Medical Centre, Liskaser *et al*,[19] have conducted a study of acid-base status associated with cardiopulmonary bypass. The bypass circuit was either primed with Haemaccel (Behring) and Ringers Injection (Baxter) or Plasmalyte 148 (table 1). For both primes the change in base excess was similar immediately following initiation of bypass. However at the end of the surgery the Plasmalyte group had a median + 1.1 mmol/L change in base excess and the Haemaccel/Ringers group had a median base excess change of - 1.5 mmol/L from pre-bypass base excess levels. These data further support the proposition that metabolism of infused solution electrolytes can attenuate the post infusion acidosis.

**The Stewart approach**

A different approach to acid-base physiology and pathophysiology has come from the work of the late Peter Stewart[20,21] (Stewart approach). This approach has had increasing attention in the critical care, anaesthesia and physiology literature[8,22,23] although it has its detractors.[24] Stewart's ideas are difficult to quickly summarize but centre around three independent factors: the partial pressure of carbon dioxide, the strong ion difference and the total concentration of weak acid. The hypothesis central to the current discussion is that the 'metabolic' component of acid-base physiology is not dependent on bicarbonate but instead, predominately on the strong ion difference.

A strong ion is defined as a completely dissociated ion in solution. The strong ion difference is defined as the sum of the concentration of strong cations minus the sum of the concentration of the strong anions (Na + K + Mg + Ca - Cl) in milliequivalents per litre (meq/L). Stewart proposed that, as the strong ion difference becomes smaller, the plasma pH falls. The dissociation of plasma water is proposed as one source of hydrogen ions. Changes in bicarbonate are seen as secondary to changes in the three independent factors.

The Stewart approach does not suggest that the clinical use of the Henderson-Hasselbalch approach in assessing acid-base status is wrong in terms of metabolic versus respiratory acid-base abnormalities. Instead, Stewart suggested that the traditional Henderson-Hasselbalch explanation of the underlying physiology and pathophysiology is wrong.

From a physiological perspective, the Stewart approach has a number of appealing features. First, the control of acid base and water homeostasis can be both explained in terms of sodium and chloride regulation. Second, acid-base is described in terms of a number of plasma electrolytes notably sodium and chloride which can be manipulated in the clinical setting to optimise acid-base status. Further, from an acid-base mechanism point of view, criticisms of the Henderson-Haselbalch approach include a lack of independence between carbon dioxide and bicarbonate and that the Henderson-Hasselbalch approach does not allow assessment of non-volatile buffers.[25] The Henderson-Hasselbalch approach can describe the equilibrium acid-base point in terms of one buffer system (bicarbonate-carbon dioxide), where several are present, because of the isohydric principle.[26] The isohydric principle applies to multiple buffers interacting in one pool of hydrogen ions such as extracellular fluid. The ioshydric principle states that: all the buffers will be in equilibrium with the hydrogen ions and each other. In Henderson-Hasselbalch terms:

$pH = pKa_1 + \log [A^-_1]/[HA_1] = pKa_2 + \log [A^-_2]/[HA_2] \ldots$ .

Therefore, although the system dynamics will involve all buffers, the end point can be described by one buffer and will obscure the role played by other buffer systems. In the Stewart approach the phosphate and protein buffers (weak acids) can be easily and explicitly included.[27]

Comparison of the Stewart and Henderson-Hasselbalch approaches is difficult as both adequately describe the acid-base end point. Further study is required to determine which approach better describes the mechanisms of acid-base physiology.

**Stewart and post infusion acidosis**

In applying the Stewart approach to post infusion acidosis, the suggested mechanism would be that normal saline and mannitol both have a strong ion difference of zero and that infusion with these solutions would reduce the plasma strong ion difference. These will be exponential processes with the plasma sodium concentration initially 35-45 mmol/L greater than the plasma chloride concentration. With saline, for each litre of saline administered, the rate of increase in chloride concentration will be greater than the rate of increase in sodium concentration (Figure 2). Conversely with mannitol the rate of fall in sodium concentration will be greater than the rate of fall in chloride concentration. This was the finding in the study by

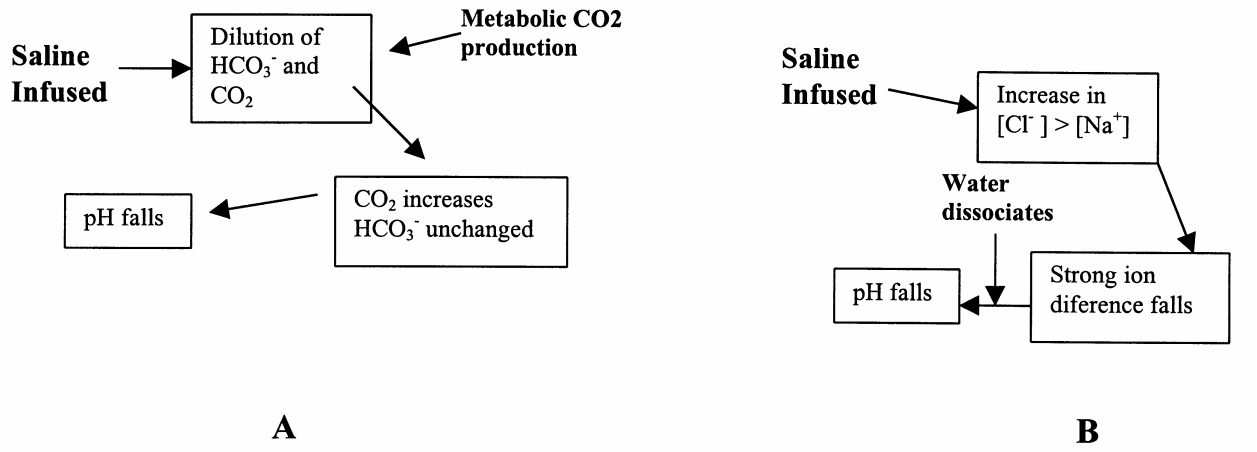


**Figure 2.** Schema comparing the Henderson-Hasselbalch (A) and Stewart (B) approaches in explaining acidosis following infusion of saline

Makoff *et al.*[14] In a previous study the same group[28] found minimal changes in acid-base status following isotonic saline infusion in nephrectomized dogs. They speculated that hyperosmolality may have affected release of bicarbonate intracellularly. From a Stewart perspective, the explanation would be that hyperosmolality affected strong ion levels across cell membranes.[29]

Although these data do not exclude the Henderson-Hasselbalch approach, the pathophysiology of post infusion acidosis is undergoing increasing debate and I believe the term dilutional acidosis should be avoided at present.

With respect to anions such as lactate, acetate and gluconate, Stewart pointed out that in solution at pH 7.4, these anions are about 4 pH units from their pKa and thus highly dissociated. Therefore, these anions can be treated as strong ions. From the Stewart point of view, once these anions are removed from the extra-cellular fluid, the strong ion difference should increase and the pH should rise. That is, the effect is not dependent on the metabolic production of bicarbonate, but instead on increasing the strong ion difference.

The change in acid-base status following lactate administration allows a comparison of the Stewart and Henderson-Hasselbalch approaches. The Stewart approach would be supported by an alkalinizing effect of a lactate solution occurring prior to the apparent metabolic bicarbonate production. In 1931 Hartmann and Senn[30] conducted a limited study in children which suggested the release of bicarbonate from lactate metabolism might take from one to two hours. This finding was supported by post infusion acid-base studies in a dog model.[16] Traverso *et al*,[17] found that during post haemorrhage resuscitation the alkalinizing effect of a lactate containing solution (Ringers Lactate) was apparent 15 minutes into the infusion, well before the predicted release of bicarbonate from metabolism.

The preceding studies support the proposition that alkalization from lactate-containing solutions occurred prior to the production of bicarbonate, thus supporting the Stewart approach. The Stewart approach would in fact suggest that the effect of lactate infusion maybe two fold. First the removal of lactate from the extracellular fluid. Second, the later addition of bicarbonate into the extracellular compartment. In Stewart terms, the important issue would not be the release of bicarbonate but instead an associated increase in the strong ion difference. However, no study has specifically compared plasma lactate, bicarbonate and strong ion levels following lactate infusion. For Hartmann's solution, the alkalinizing effect would be facilitated by the lower chloride content which would tend to attenuate the reduction in the strong ion difference following infusion compared with a saline infusion.

**Clinical significance**

The clinical significance of post infusion acidosis is unclear. In a frequently cited review from the 1970s, Garella[13] speculated that post infusion acidosis would be of limited clinical significance. Several factors complicate the clinical interpretation of previous studies. One factor in this is that some of the animal models used were relatively euvolaemic and mortality could not be used as an end point. Similarly, McFarlane and Lee[18] could not compare mortality in their small groups of patients who did not have excessive blood loss.

Traverso and collegues[17] found that post haemorrhagic resuscitation in pigs led to significant metabolic acidaemia. They compared acid-base changes and survival in groups of 20 pigs following blood loss of 54 ml/kg over 15 minutes and compared resuscitation of

3 times blood loss with 0.9% saline, Ringers Lactate, Plasmalyte or Plasmalyte-R (table 1).

This group found that Ringers Lactate (Hartmann's) produced less acidosis than normal saline. In a survival analysis, they found greater survival at 24 hours in the Ringers Lactate group compared with the saline group: 67% versus 50%. Whilst this difference was clinically important (number needed to treat = 7), it was not statistically significant ($p = 0.22$).

This analysis may have had limited power due to the number of comparisons required, and further 95% confidence intervals were not calculated. Another finding by the Traverso group was that the lowest survival rates were in the two Plasmalyte groups (40% for Plasmalyte-R and 30% for Plasmalyte). The authors speculated that magnesium and/or acetate may play a role in this worse outcome.

This suggestion highlights the need to consider the non acid-base roles of the electrolytes in crystalloid solutions. Another complicating factor is the suggestion that hypertonic solutions may alter cell membrane function via an effect of hypertonicity.

In summary, there is currently much debate about the actual nature of acid-base physiology and patho-physiology. Post infusion acidosis is an area which highlights this debate. Limited animal studies and clinical reports suggest that fluid replacement following massive blood loss is associated with significant metabolic acidosis. The use of solutions such as Hartmann's instead of saline is likely to attenuate this acidosis and may improve outcome.

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