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Effects of intravenous solutions on acid-base equilibrium: from crystalloids to colloids and blood components

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Abstract

Intravenous fluid administration is a medical intervention performed worldwide on a daily basis. Nevertheless, only a few physicians are aware of the characteristics of intravenous fluids and their possible effects on plasma acid-base equilibrium. According to Stewart's theory, pH is independently regulated by three variables: partial pressure of carbon dioxide, strong ion difference (SID), and total amount of weak acids (A_{TOT}). When fluids are infused, plasma SID and A_{TOT} tend toward the SID and A_{TOT} of the administered fluid. Depending on their composition, fluids can therefore lower, increase, or leave pH unchanged. As a general rule, crystalloids having a SID greater than plasma bicarbonate concentration (HCO_3^-) cause an increase in plasma pH (alkalosis), those having a SID lower than HCO_3^- cause a decrease in plasma pH (acidosis), while crystalloids with a SID equal to HCO_3^- leave pH unchanged, regardless of the extent of the dilution. Colloids and blood components are composed of a crystalloid solution as solvent, and the abovementioned rules partially hold true also for these fluids.

The scenario is however complicated by the possible presence of weak anions (albumin, phosphates and gelatins) and their effect on plasma pH. The present manuscript summarises the characteristics of crystalloids, colloids, buffer solutions and blood components and reviews their effect on acid-base equilibrium. Understanding the composition of intravenous fluids, along with the application of simple physicochemical rules best described by Stewart's approach, are pivotal steps to fully elucidate and predict alterations of plasma acid-base equilibrium induced by fluid therapy.

Key words: acid-base equilibrium, Stewart's approach, intravenous infusions, crystalloids, colloids, albumin, blood components

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William B. O'Shoughnessy, a 22-year-old medical graduate of Edinburgh University, was allegedly one of the first physicians to think about intravenous fluid therapy [1, 2]. Indeed, during the British pandemic of Indian cholera of 1831-32, he thoroughly studied patients who suffered from the disease, describing that "*the blood drawn in the worst cases had lost a great proportion of its water and neutral saline ingredients*". He concluded that the therapy should "*restore the blood to its specific gravity and restore the deficient saline matters*" which could be achieved through "*absorption, imbibition or by direct injection of aqueous fluids into the veins*". Shortly thereafter, Thomas Latta, a physician from Leith near Edinburgh, applied O'Shoughnessy's reasoning. He inserted a tube into the basilic vein of an aged, moribund woman, and injected "*six pints*" of saline solution intravenously. The solution supposedly consisted of 58 mEq L^{-1} of sodium ($Na+$), 49 mEq L^{-1} of chloride (Cl^-) and 9 mEq L^{-1} of bicarbonate (HCO_3^-). The patient recovered, initially, "*the pulse*

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returned to the wrist and her extremities were again warm", so that the enthusiastic and exhausted Latta left the lady in the care of the hospital's surgeon. The patient however relapsed quickly thereafter and died a few hours later.

As usually happens, there is no universally accepted version of history, and there is considerable uncertainty as to how we progressed from that first pioneering experience to the crystalloid solution that is mostly used nowadays, namely 0.9% NaCl, also known as '*normal*' or '*physiologic*' saline solution. Some researchers have identified Hartog Hamburger, a Dutch physiologist of the 19th century, as the forgotten, and probably unaware, father of 0.9% NaCl. It might be of interest to underline that Hamburger had proposed this type of solution for his *in vitro* studies, in order to avoid red blood cell lysis [3] and certainly not as an *in vivo* formulation. Be that as it may, since that time many things have changed in medicine, and nowadays several types of fluids are available for intravenous therapy. Despite the clear role of intravenous fluids for the treatment of hypovolemia, their potential to cause even marked acid-base derangements has long been recognised [4].

In the following manuscript, we will review the use of different types of intravenous fluids, focusing our attention on their effect on plasma acid-base and electrolyte equilibrium. We will separately analyse the effects of (i) crystalloid solutions, (ii) solutions containing natural and synthetic colloids, (iii) so called 'buffer solutions' or 'alkalinising agents' and (iv) blood components, basing our reasoning on Stewart's approach to acid-base and electrolyte equilibrium [5, 6] which is briefly summarised below.

STEWART'S APPROACH: PRINCIPLES OF ACID-BASE EQUILIBRIUM

The analysis of acid-base chemistry presented by Peter Stewart focuses its attention on aqueous solutions, and explicitly starts from the following simple question [6]: what is that determines hydrogen ion concentration (and thus pH) in an aqueous solution? Addressing this question with a thorough mathematical and physicochemical analysis, Stewart first described the factors of interest in this process: (i) the solvent, which is water; (ii) strong ions, substances being always entirely dissociated in aqueous solutions (such as Na^+, K^+, Cl^-); and (iii) weak ions, substances being only partially dissociated in aqueous solutions, according to their dissociation constant (such as plasma albumin).

Subsequently, Stewart set up and solved a system of equations, which describe the interplay between these factors in dictating the *dependent* variable pH and identified three variables that *independently* regulate pH:

1. PCO_2: the partial pressure of carbon dioxide;
2. A_{TOT}: the concentration of non-volatile weak acids (mainly albumin and phosphate in the extracellular space);

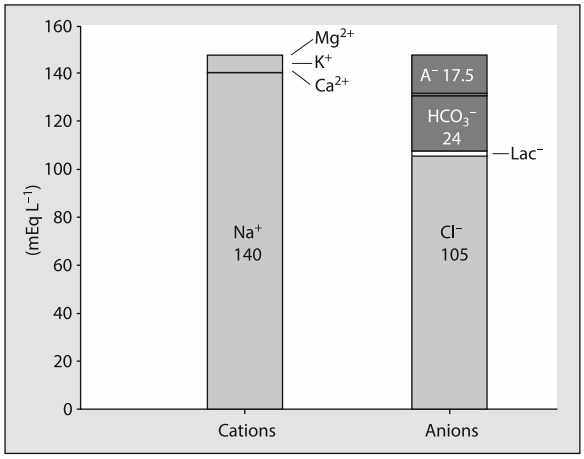

Figure 1. Normal gamblegram of plasma**.** Schematic representation of the gamblegram of normal plasma. The total concentration of cations and anions must always be equal in order to preserve electrical neutrality. All concentrations are expressed in mEq L^{-1}. Strong cations: Na+ (140), K^+ (4), Mg^{++}(1), Ca^{++} (2.5); strong anions: Cl^- (105), Lac^- (1); weak anions: HCO_3^- (24), A^- (17.5). The concentrations of H^+ and OH^- are quantitatively irrelevant and are therefore not shown

3. SID: the strong ion difference, defined as the difference between the sum of concentrations of all strong cations (mainly Na^+, K^+, Mg^{2+}, Ca^{2+}) and the sum of concentrations of all strong anions (mainly Cl^- and lactate).

Variations in these three independent variables have a direct effect on pH. PCO_2, which is strictly related to alveolar ventilation, leads to acidosis (and therefore a decrease in pH) when its value increases, whereas it leads to alkalosis (and therefore an increase in pH) when its value decreases. A_{TOT} (and its dissociated form, A^-), shifts pH toward acidosis when its value increases, whereas it shifts pH toward alkalosis when its value decreases. SID leads to acidosis when its value decreases, whereas it leads to alkalosis if its value increases. The SID, in fact, dictates the gap of charges within the anionic portion of the Gamblegram (see Fig. 1) that needs to be filled in by weak anions (A^-, HCO_3^- and minimal concentrations of OH^-) in order to preserve electrical neutrality.

CRYSTALLOIDS

Crystalloids are aqueous solutions containing mineral salts and/or salts of organic acids. By definition, crystalloids do not contain albumin and/or phosphates and the infusion of any type of crystalloid therefore causes a reduction in A_{TOT}. The entity of the reduction of A_{TOT} depends on the extent of the dilution, and therefore on the amount of infused crystalloid. As discussed above, the reduction of plasma *weak acids*, A_{TOT}, has *per se* an alkalinising effect.

At the same time, every crystalloid solution is characterised by a Strong Ion Difference, SID*inf*, that ranges, for commercially available solutions, between 0 and 55 mEq L^{-1}

Table 1. Characteristics of the principal crystalloid solutions

	NaCl 0.9%	Lactated Ringer's	Acetated Ringer's	Hartmann's solution	Rehydrating III	Rehydrating I	PlasmaLyte	Sterofundin ISO	Dextrose 5%	Dextrose 5% in NaCl 0.45%
Na^+ (mEq L^{-1})	154	130	132	131	140	126	140	145	0	77
K^+ (mEq L^{-1})	154	4	4	5	10	36	5	4	0	0
Ca^{2+} (mEq L^{-1})	0	3	3	4	5	0	0	5	0	0
Mg^{2+} (mEq L^{-1})	0	0	0	0	3	0	3	2	0	0
Cl^- (mEq L^{-1})	0	109	110	111	103	104	98	127	0	77
Lactate (mEq L^{-1})	0	28	0	29	0	52	0	0	0	0
Acetate (mEq L^{-1})	0	0	29	0	47	0	27	24	0	0
Citrate (mEq L^{-1})	0	0	0	0	8	0	0	0	0	0
Malate (mEq L^{-1})	0	0	0	0	0	0	0	5	0	0
Gluconate (mEq L^{-1})	0	0	0	0	0	0	23	0	0	0
Dextrose (mmol L^{-1})	0	0	0	0	0	0	0	0	260	260
In-vivo SID (mEq L^{-1})	0	28	29	29	55	52	50	29	0	0
Caloric content (kcal L^{-1})	0	9	6	9	11	17	21	6	170	170
CO_2 from 1 L solution (L)	0.0	1.9	1.3	2.0	2.5	3.5	4.3	1.5	35.0	35.0

All solutions have an *in vitro* SID of 0 mEq L^{-1}. However, the solutions containing organic anions have an *in vivo* SID that equals the sum of the organic anions (ranging between 27 and 55 mEq L^{-1}), once the organic anions are metabolised (see text for details). Metabolism implies oxygen consumption and CO_2 production: 'CO_2 produced from 1 L solution' represents the theoretical CO_2 production deriving from complete oxidation of organic anions and from glucose (see also Table 3).

(Table 1). Of note, there might be a significant difference between the *in vitro* SID and the *in vivo* SID, i.e. the resulting SID after the metabolism of organic anions (see Table 2 and text below in the paragraph '*organic anions*'). The infusion of crystalloid solutions will dilute the extracellular volume (plasma and interstitium), and the extracellular SID will tend toward the SID*inf*, the SID of the administered crystalloid. For example, infusing NaCl 0.9%, *normal saline*, which has a SID*inf* of 0 mEq L^{-1} will *always* reduce plasma SID as a SID of 0 mEq L^{-1} will *always* be lower than plasma SID of a biological living system. On the other hand, administering a crystalloid with a high SID*inf*, e.g. 50 mEq L^{-1} to a patient with a plasma SID of 40 mEq L^{-1}, will result in an increase in plasma SID. As discussed above, a reduction in SID has an acidifying effect, while an increase in SID has an alkalinising effect.

The infusion of a crystalloid solution therefore potentially alters two of the three independent variables that regulate acid-base equilibrium: A_{TOT} and SID. In theory, also the partial pressure of carbon dioxide (PCO_2) could change during the infusion of crystalloids; however, for the sake of clarity, we will refer to isocapnic dilutions, i.e. infusion of fluids performed at constant PCO_2 [7].

Based on these assumptions, it is clear that, in contrast to the classical theory of bicarbonate dilution with resulting *dilutional acidosis* [8,9], the acid-base derangement following crystalloid infusions will depend upon the physicochemical characteristics of the administered fluid [10]. The crystalloid solution that does not, regardless of the degree of plasma dilution, alter plasma pH, should therefore balance the alkalinising effect of A_{TOT} dilution with a corresponding reduction in SID, which is usually achieved through an increase in chloride concentration. In normal conditions of acid-base equilibrium, i.e. pH 7.40, PCO_2 = 40 mm Hg, HCO_3^- = 24 mEq L^{-1}, such crystalloid has been found to be a solution having a SID*inf* = 24 mEq L^{-1} [11–13]. Thinking about an infinite dilution of plasma helps to understand this concept. An infinite dilution will bring A_{TOT} to zero, and plasma SID will eventually equal SID*inf*. Electrical neutrality will be assured by HCO_3^- ions that will therefore equal SID*inf*, i.e. they will be 24 mEq L^{-1}. If PCO_2 and HCO_3^- will remain unchanged as before the dilution, the resulting pH, in accordance with Henderson and Hasselbalch's equation, will not change.

In medicine, several conditions are however characterised by gross abnormalities in acid-base equilibrium, one of the most meaningful examples being chronic respiratory failure. This condition is characterised by constantly elevated PCO_2 values, frequently between 60–80 mm Hg, low plasma chloride concentrations with associated increased SID (frequently as high as 50–60 mEq L^{-1}), high bicarbonate concentrations (30–40 mEq L^{-1}), and close to normal pH

values. In such a condition, the infusion of a crystalloid having a SID*inf* of 24 mEq L^{-1}, which normally affects pH only slightly, would have a strongly acidifying effect. As an example, if we consider a patient having PCO_2 = 80 mm Hg, HCO_3^- = 44 mEq L^{-1} and pH = 7.36, and hypothesise an infinite dilution with SID*inf* = 24 mEq L^{-1}, eventually we will have the same PCO_2, HCO_3^- = 24 mEq L^{-1} (equal to SID*inf*), and a pH of roughly 7.10. If, on the other hand, SID*inf* will be 44 mEq L^{-1}, i.e. equal to the *baseline* concentration of HCO_3^-, then there would be no change in pH, regardless of the extent of the dilution. This hypothesis has been demonstrated both in a mathematical model and *in vitro* and *in vivo* studies [14, 15]. So, the general rule regulating pH variations during isocapnic crystalloid infusions seems to be the following:

1. If SID*inf* > *baseline* HCO_3^-, then pH tends toward an alkalosis.
2. If SID*inf* < *baseline* HCO_3^-, then pH tends toward an acidosis.
3. If SID*inf* = *baseline* HCO_3^- , then pH will not change, regardless of the extent of the dilution.

It might however be important to mention a few additional factors. Firstly, different electrolytes have different distribution compartments. Sodium, for example, remains almost entirely in the extracellular volume, and so does chloride. Potassium, on the contrary, mainly enters the cells, being the intracellular potassium concentration very high, around 140 mEq L^{-1} and the strictly regulated extracellular potassium concentration only about 4–5 mEq L^{-1}. It is therefore conceivable that the acid-base effect of solutions containing potassium is slightly lower than that of a crystalloid solution having the identical SID*inf* resulting only from sodium and chloride. Secondly, osmolarity is an additional factor that might contribute to the effects of crystalloid infusions on plasma acid-base equilibrium by shifts of water from the intracellular to the extracellular volume, or *vice versa* (see below). Furthermore, as the *in vivo* effect requires organic anions to be metabolised, a high rate of crystalloid infusion could, in theory, cause an organic ion load that exceeds its metabolism, resulting in its accumulation. In the presence of normal liver and renal function, this is however a purely theoretical condition. Finally, *in vivo*, the healthy kidney reacts rapidly to the induced acid-base derangements limiting their extent through the modulation of volume and electrolyte excretion [16, 17]. Of course, this implies that these effects can be amplified in the case of kidney injury/failure.

Based on the abovementioned reasoning, the term 'balanced solutions' was introduced in order to define solutions that have electrolyte concentrations close to those of plasma [18]. Lactated Ringer's, PlasmaLyte, Sterofundin, Acetated Ringer's and Hartmann's solution (Table 1) can be included in this category. Regarding the effect on plasma acid-base equilibrium in a normal subject (HCO_3^- = 24 mEq L^{-1}), Lactated Ringer's and Sterofundin perform better, as their *in vivo* SID is closer to the baseline concentration of HCO_3^- compared to PlasmaLyte. On the other hand, PlasmaLyte and Lactated Ringer's are 'more balanced' regarding their chloride concentration (98 and 109 mEq L^{-1}, respectively) and they therefore probably induce less hyperchloremia compared to Sterofundin (127 mEq L^{-1} of chloride). Of note, a chloride-restrictive fluid administration has been found to be associated with a lower incidence of acute kidney injury and use of renal replacement therapy, compared to a chloride-liberal one [19].

ORGANIC ANIONS

Table 1 shows that some crystalloids include organic anions in their composition. There are many reasons for substituting chloride with organic anions in crystalloid solutions. On the one hand, organic anions are more stable than bicarbonate ions and the tendency to atmospheric equilibration, with consequent increase in pH, is therefore reduced [20]). On the other hand, by providing organic strong negative charges, the presence of organic anions allows the lowering of the chloride concentration of the solution while maintaining sodium concentration, osmolarity and electrical neutrality.

All the employed organic anions have pKa values that are below normal plasma pH (Table 2), meaning that in solution they are almost completely dissociated, and can therefore be considered as strong anions (see above). It must however be noted that the *in vitro* SID of these solutions is always equal to 0 mEq $L^{-1}$and therefore does not differ from 0.9% NaCl [7]. On the contrary, once these fluids are infused intravenously, the organic anions are promptly transferred into the cells where they are metabolised. This metabolic effect has two results: (i) the *in vivo* SID increases and equals, in case of complete metabolism, the concentration of the organic anion in the solution; and (ii) oxygen is consumed and CO_2 produced, i.e. the calories deriving from the organic anions are 'burned'. Table 2 summarises the caloric content of frequently used crystalloid solutions and the CO_2 that would be produced by complete oxidation of the organic anions contained in 1 L of solution. Part of the produced CO_2 will be hydrated to HCO_3^- and 'fill in the gap' to ensure electroneutrality, and part of it will be exhaled through the lungs (Fig. 2).

The most commonly used solution containing an organic anion is Lactated Ringer's which contains 28 mmol L^{-1} of L-Lactate. In the absence of severe liver dysfunction, L-lactate can be metabolised at high rates (up to 100 mmol h^{-1}) by oxidation and/or gluconeogenesis [21, 22]. Thus it has been estimated that up to 3–4 L of Lactated Ringer's can be administered per hour in an average-weight adult patient without expecting significant lactate accumulation. The

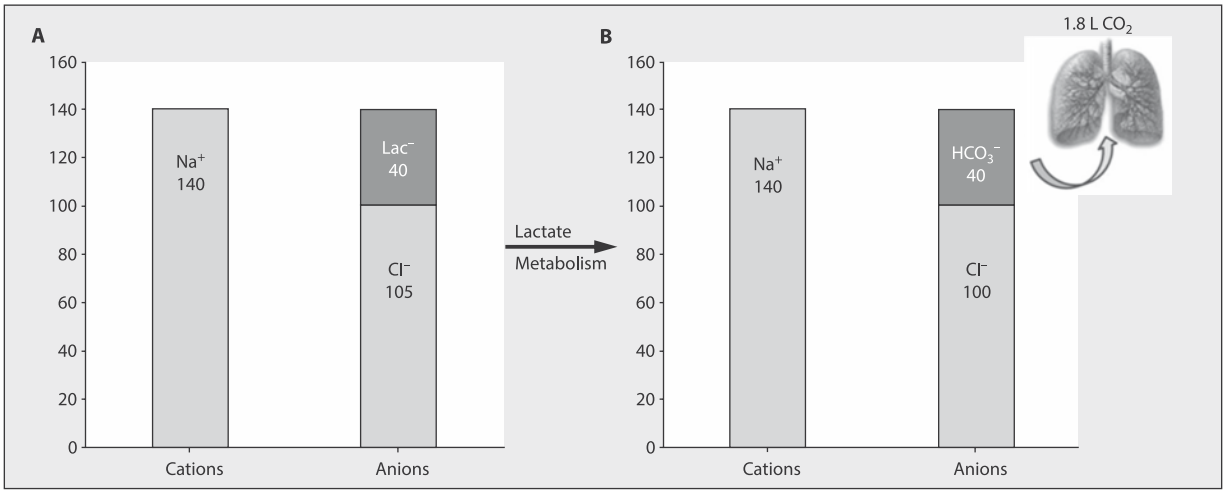

Figure 2. Schematic representation of the effect of lactate metabolism on CO_2 production; **A** — gamblegram of a solution consisting of 140 mEq L^{-1} of sodium, 100 mEq L^{-1} of chloride and 40 mEq L^{-1} of lactate. Lactate metabolism has not yet taken place; **B** — gamblegram of the same solution after lactate metabolism. Lactate is completely replaced by HCO_3^-. In a case of complete oxidation, 3 millimoles of CO_2 are produced from every metabolised millimole of lactate. This means that two thirds of the produced CO_2 (~1,800 mL) needs to be exhaled through the lungs and one third (~900 mL) remains in the system in its hydrated form, HCO_3^-

Table 2. Characteristics of the organic anions employed in crystalloid solutions

	Molecular formula	Molar mass (g mol^{-1})	pKa	Kcal $mmol^{-1}$	CO_2 (mmol)/mmol	CO_2 (mL)/mmol
Glucose	$C_6H_{12}O_6$	180	–	0.72	6	134
Lactate	$C_3H_5O_3^-$	89	3.86	0.32	3	67
Acetate	$C_2H_3O_2^-$	60	4.76	0.20	2	45
Citrate	$C_6H_5O_7^{3-}$	189	3.14–4.77–6.39	0.47	6	134
Malate	$C_4H_4O_5^{2-}$	134	3.4–5.11	0.34	4	90
Gluconate	$C_6H_{11}O_7^-$	196	3.86	0.68	6	134

Definition of abbreviations: pKa = negative logarithm of the dissociation constant; Kcal/mmol = caloric content per mmol of organic anion; CO_2 (mmol)/mmol = theoretical millimoles of CO_2 produced from complete oxidative metabolism of 1 mmol of organic anions; CO_2 (mL)/mmol = theoretical millilitres of CO_2 produced from complete oxidative metabolism of 1 mmol of organic anions. Of note, *in vivo* CO_2 production is lower than reported, as part of the organic anions take different metabolic pathways, e.g. gluconeogenesis, that produce less CO_2. Malate and citrate are diprotic and triprotic acids, respectively. For this reason, two and three values of pKa are shown

metabolic pathway undertaken by lactate depends on the metabolic status and insulin concentration of the patient. On average, 50–70% of lactate is oxidised to CO_2 while the rest undergoes gluconeogenesis [21, 22]. A major advantage of lactate compared to other employed organic anions is the possibility of performing bedside point-of-care measurements of its concentration.

Citrate is contained in some crystalloid solutions. The complete oxidation of one mole of citrate yields six moles of CO_2. It is however worth underlining that citric acid is a triprotic acid (three different values of pKa in Table 2), i.e. in our case each molecule of citrate binds to three sodium cations ($Na_3C_6H_5O_7$). In this respect, the moles of CO_2 produced for every mole of sodium in the solution are two. Citrate has a strong chelating effect on calcium. While this feature has probably limited its use in crystalloid solutions, the ensuing anticoagulant effect is exploited for regional anticoagulation during continuous renal replacement therapy and in the preparation of blood products (see 'Blood components' below).

Acetate is another commonly employed organic anion and it has some advantages over lactate. Firstly, its metabolism has been estimated to be three times faster than that of lactate [23], with virtually no accumulation risk due to its extensive extrahepatic metabolism. Moreover, the complete oxidation of one mole of acetate produces only two moles of CO_2. Characteristics of gluconate and malate are reported in Table 2.

In summary, the lowest production of CO_2 would be achieved by using either acetate or citrate as chloride-substituting organic anions. However, because of citrate's calcium chelating effect, only acetate containing solutions can be designed and safely administered. In conclusion, the characteristics of acetate (quick metabolism, low CO_2 production) and lactate (quick metabolism, possibility of performing bedside

point-of-care measurements) justify their widespread use as substituting organic anions in crystalloid solutions.

OSMOLARITY

Normal plasma osmolarity ranges between 285 and 295 mOsm L^{-1} and is schematically due to sodium salts in the extracellular volume (~40% of total body water) and to potassium salts in the intracellular volume (~60% of total body water). When a crystalloid solution is administered intravenously, the infused fluid will distribute evenly in the different compartments of the extracellular volume, ~20% in plasma and ~80% in the interstitium. In the case of an isoosmotic crystalloid solution, this will not alter plasma osmolarity, but simply expand the extracellular space. However, if the osmolarity of the infused crystalloid is significantly higher than plasma osmolarity, there will be a shift of free water from the intracellular volume to the extracellular volume in order to reach an osmolar equilibrium. This, in turn, will result in an additional dilution of the extracellular volume by means of free water (which has a SID o 0 mEq L^{-1}), and therefore an additional acidifying effect compared to a solution with the same SID having an osmolarity similar to plasma [24]. On the contrary, the infusion of a hypoosmotic solution will reduce plasma osmolarity, requiring a shift of free water from the extracellular to the intracellular volume. Of note, the subtraction of free water from a solution results in the increase in plasma SID that is not compensated for by the associated increase in A_{TOT} caused by dehydration. The net effect is therefore an alkalinisation of plasma as demonstrated in *in vitro* evaporation experiments [25, 26]. Table 3 summarises the osmolarity of commercially available solutions and the effect on plasma expansion of 1 L of each solution.

ABSORPTION OF FREE WATER

The intravenous infusion of free water, characterised by a SID of 0 mEq L^{-1} and an osmolarity of 0 mOsm L^{-1}, should be avoided as it could cause haemolysis. However, there are particular clinical conditions in which this event may partially occur. For instance, a significant absorption (up to 5,000 mL) of 'irrigation fluid', often consisting of distilled water [27], may occur during transurethral resection of the prostate (TURP). The ensuing 'TURP syndrome' is characterised by dilution of plasma with distilled water resulting in a reduction in all electrolyte concentrations with ensuing reduction in SID and A_{TOT}. The net effect is a metabolic acidosis [28]. Of note, this acidosis will be a 'hypochloremic acidosis'. Furthermore, as discussed above, the infusion would have a less acidifying effect compared to an isovolumetric dilution with NaCl 0.9%, as part of the water would enter the intracellular volume, therefore not contributing to the dilution of plasma and interstitial volume.

Table 3. Osmolarity and plasma expansion of crystalloids

Intravenous solutions	Osmolarity (mOsm L^{-1})	Plasma expansion mL (%)
Distilled water	0	40 (2.4)
NaCl 0.45%	154	144 (4.3)
Dextrose 5%	260	188 (5.6)
Lactated Ringer's	274	194 (5.8)
Acetated Ringer's	278	195 (5.8)
Hartmann's solution	279	196 (5.8)
PlasmaLyte	294	201 (6.0)
Rehydrating III	307	207 (6.2)
NaCl 0.9%	308	207 (6.2)
Sterofundin	309	208 (6.2)
Rehydrating I	312	209 (6.2)
Dextrose 5% in NaCl 0.45	414	250 (7.4)
Mannitol 10%	549	303 (9.0)
NaCl 3%	1,026	481 (14.3)
Mannitol 20%	1,100	507 (15.1)
NaCl 5%	1,712	716 (21.3)
$NaHCO_3$ 8.4%	2,000	808 (24.0)
NaCl 7.5%	2,565	978 (29.1)

Fluids are listed by increasing osmolarity (as reported by the manufacturer). Theoretical increase in plasma volume resulting from the infusion of 1 L of solution (absolute, in mL, and as percentage of plasma volume) of a patient weighing 70 kg, having a plasma osmolarity of 290 mOsm L is reported. The mathematical model assumes a ratio between plasma and interstitial volume of 0.25 and does not consider losses of volume and electrolytes through kidney excretion. The infusion of 1 L of iso-osmotic solution (290 mOsm in this example) causes a plasma expansion of 200 mL. Hyperosmotic solutions (> 290 mOsm L^{-1}) cause a greater increase in plasma volume that is caused by the shift of free water (SID = 0 mEq L^{-1}) from the intracellular to the extracellular space. On the other hand, hypoosmotic solutions (< 290 mOsm L^{-1}) show a reduced plasma expansion as some free water moves from the extracellular to the intracellular space

COLLOIDS

Colloids are aqueous solutions containing oncotic macromolecules. The carriers/solvents of these macromolecules are in fact crystalloid solutions, i.e. they contain mineral salts with/without organic anions, and are therefore characterised by a SID*inf* (Table 4). Colloids can be divided into two categories: synthetic (starches, gelatins and dextrans); and natural, or derived from plasma (albumin). Furthermore, from an acid-base perspective colloidal molecules can be distinguished as being electrically charged, ionic colloids, therefore belonging to the category of weak acids, A_{TOT} (albumin and gelatins), or not being electrically charged, nonionic colloids (starches and dextrans).

Nonionic colloids follow the mechanisms described above for crystalloid solutions. As can be seen in Table 4, many starches and dextrans are based on 0.9% NaCl, and therefore have a SID of 0 mEq L^{-1}. Their effect on acid-base equilibrium is therefore similar to that of *normal saline* [29, 30]. Hextend® (BioTime, Inc., Berkeley, CA, USA) and

Table 4. Composition of natural and synthetic colloid solutions

	Albumin		Gelatins				Starches			Dextrans
	4%	20%	Haemaccel	Gelofusine	Isoplex	Gelaspan	Pentaspan	Hextend	Tetraspan	Dextran 70
Albumin (g L^{-1})	40	200	-	-	-	-	-	-	-	-
Gelatin (g L^{-1})	-	-	35[a]	40[b]	40[b]	40[b]	-	-	-	-
HES (g L^{-1})	-	-	-	-	-	-	100	60	60	-
Dextran (g L^{-1})	-	-	-	-	-	-	-	-	-	60
Na^+ (mEq L^{-1})	140	~130	145	154	145	151	154	143	140	154
K^+ (mEq L^{-1})	-	-	5.1	-	4	4	-	3	4	-
Ca^{2+} (mEq L^{-1})	-	-	12.5	-	-	2	-	5	5	-
Mg^{2+} (mEq L^{-1})	-	-	-	-	1.8	2	-	0.9	2	-
Cl^- (mEq L^{-1})	128	77	145	120	105	103	154	124	118	154
Lactate (mEq L^{-1})	-	-	-	-	25	-	-	28		-
Malate (mEq L^{-1})	-	-	-	-	-	-	-	-	5	-
Acetate (mEq L^{-1})	-	-	-	-	-	24	-	-	24	-
Octaonate (mEq L^{-1})	6.8	16	-	-	-	-	-	-	-	-
Acetyltriptophane	0	16	-	-	-	-	-	-	-	-
SID (mEq L^{-1})	12	~53	17.6	34	45.8	56	0	28	29	0

Characteristics of some colloid solutions frequently employed in clinical practice. Compositions are reported as declared by the manufacturer. Of note, electrolyte compositions of albumin-containing fluids differ between brands. Examples are reported in table: Albumin 4% refers to Albumin 4%, CSL Biotherapies, Australia; Albumin 20% to Uman Albumin 200 g L^{-1}, Kedrion, Italy; Pentaspan to 10% Pentastarch, Bristol-Myers Squibb, USA; Dextran 70 to 6% Dextran 70 in 0.9%NaCl, Bbraun Melsungen, Germany. Other brands are reported in the main text. SID refers to SID after metabolism of organic anions (lactate, malate, acetate, octanoate); SID of albumin preparations is greater for higher albumin concentrations (20%) due to the increased amount of albumin and resulting increase in negative charges (A^-). Gelatins are either (a) urea-linked or (b) succynilated (the latter provide a greater amount of negative charges due to increased dissociation). Starches and dextrans are nonionic colloids, i.e. their molecules do not contain negative charges

Tetraspan® (Bbraun Melsungen, Germany), among others, are so-called 'balanced starches', as part of the chloride has been substituted with organic anions. As a result, these colloids have an *in vivo* SID*inf*, after the metabolism of organic anions, of around 28 mEq L^{-1}, and should follow the rules set out above (see 'Crystalloid solutions'). Among the typical characteristics of starches, i.e. concentration, molecular weight and molar substitution [31], only the first should have a possible effect on acid-base equilibrium as it determines differences in the osmolarity of the solution (*see above*).

Gelatins are proteins derived from thermal degradation of collagen derived from cattle bones [32]. Gelatins can be either small and globular polypeptide chains that are cross-linked by urea bridges and are characterised by less negative charges, urea-linked gelatins (Haemaccel, Hoechst, Australia), or characterised by long stretched polypeptide chains and an increased amount of negative charges created by succinylation, succinylated gelatins (Gelaspan and Gelofusine, Bbraun Melsungen AG, Germany; Isoplex, Beacon Pharmaceuticals, UK). Haemaccel and Gelofusine induce a metabolic acidosis similar to the one of 0.9% NaCl, but characterised by a significant increase in non-measured anions and therefore in Strong Ion Gap (SIG), which can be explained by the negative charges of the polygeline molecules [33, 34]. The effects

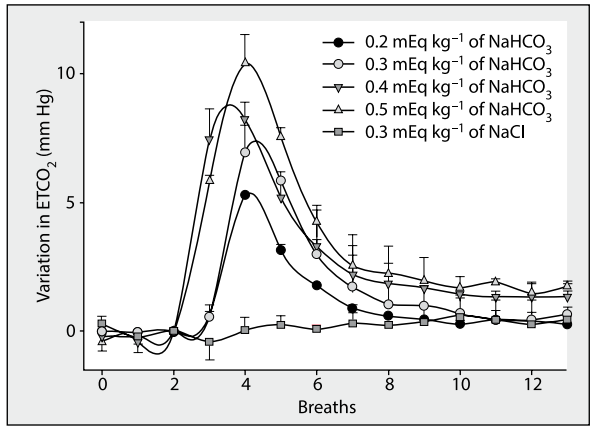

Figure 3. Effect of injections of sodium bicarbonate and sodium chloride on end-tidal CO_2. Breath by breath variations in end-tidal CO_2 ($ETCO_2$) caused by the bolus injection of different amounts (0.2–0.5 mEq kg^{-1}) of a molar sodium bicarbonate solution (8.4% $NaHCO_3$) and by the bolus injection of 0.3 mEq of a molar solution of sodium chloride (5.84% NaCl). Symbols and error bars represent mean ± standard deviation. Original experimental data acquired on three healthy piglets (22 ± 1 kg). Pigs were anaesthetised, paralysed and mechanically ventilated with tidal volume of 10 mL kg^{-1} and respiratory rate of 15

of Isoplex and Gelaspan have not yet been directly verified. However, having an *in vivo* SID*inf* deriving both from the metabolism of organic anions and gelatin's charges,

these solutions should have a less acidifying effect compared to Gelofusine and Haemaccel.

Albumin contained in solutions is derived from human plasma. There are several commercially available preparations, mainly with albumin concentrations of 4% and 20% (examples are summarised in Table 4). Of note, the electrolyte composition of the solvent, and therefore its SID*inf*, differs considerably between different preparations, probably due to differences in the preparation process. The acidifying effect of albumin-containing solutions having a low SID*inf* is easily understandable, as both the decrease in SID and the increase in A_{TOT} decrease plasma pH [29, 30, 34, 35] and have been found to be similar to that of normal saline [34].

BUFFER SOLUTIONS OR ALKALISING AGENTS

SODIUM BICARBONATE (IUPAC NAME: SODIUM HYDROGEN CARBONATE)

A molar solution of sodium bicarbonate (8.4% $NaHCO_3$) falls, strictly speaking, into the category of crystalloids. It is, however, a very particular crystalloid because it: (i) contains a high concentration of sodium (1,000 mEq L^{-1} of Na^+, calculated osmolarity 2,000 mOsm L^{-1}); and (ii) contains a high concentration of weak anions (1,000 mEq L^{-1} of HCO_3^-), and therefore has, both *in vivo* and *in vitro*, a SID of 1,000 mEq L^{-1}. For this reason, sodium bicarbonate is often called a 'buffer' or 'alkalinising agent'. Its use to correct pH in a case of metabolic acidosis is very controversial and still debated [36].

When a sodium bicarbonate solution is infused intravenously, a rapid increase in expired CO_2 is observed (Fig. 3). Being the amount of free H^+ buffered by HCO_3^- negligible at pH ranges of human plasma, a plausible explanation for the observed phenomenon is the following: the infused sodium ions increase plasma SID inducing a shift of plasma pH toward an alkalosis. Being the amount of dissociated non-carbonic weak acids pH dependent (see equation 1), the increased pH favours the dissociation of non-carbonic buffers. The equilibrium of equation 2 is therefore pushed to the right.

$$[A^-] = [Alb] \times (pH \times 0{,}1204 - 0{,}625) + [Pi] \times \times (pH \times 0{,}309 - 0{,}469) \quad \text{Eq. 1}$$

where $[A^-]$ is the dissociated, electrically charged part of 'non carbonic buffers' and is expressed in mEq L^{-1}, [Alb] is the plasmatic concentration of albumin expressed in g L^{-1}, [P*i*] is the plasmatic concentration of phosphates expressed in mmol L^{-1}, and pH denotes arterial pH.

$$[AH] \rightleftarrows [A^-] + [H^+] \quad \text{Eq. 2}$$

where AH is the non dissociated part of 'non carbonic buffers'.

The released hydrogen ions react with bicarbonate ions, transiently forming carbonic acid and finally separating into H_2O and CO_2 (Equation 3).

$$HCO_3^- + H^+ \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2 \quad \text{Eq. 3}$$

These mechanisms explain why a lower concentration of albumin, i.e. the major component of A_{TOT}, is associated with a lower amount of exhaled CO_2 during a sodium bicarbonate load (and *vice versa*) [37]. Furthermore, the increase in CO_2 and its entrance into the cells is considered responsible for the 'paradoxical' intracellular acidosis that has been observed during sodium bicarbonate infusion [38]. Finally, we need to keep in mind that, even though most of the CO_2 is retained in the organism, the alkalinising effect of sodium bicarbonate is complete only once the produced CO_2 has been eliminated through alveolar ventilation. For this reason, sodium bicarbonate should probably not be employed to correct respiratory acidosis, a condition in which alveolar ventilation is impaired.

TRIS-HYDROXYMETHYL AMINOMETHANE (THAM)

In an attempt to overcome these limitations, Tris-Hydroxymethyl Aminomethane (THAM) has been developed [39]. THAM is an uncharged molecule, an amino alcohol that can be defined, according to Stewart's parlance, as an '*add-on weak base*'. Indeed, THAM can become a cation by binding to H^+ (Equation 4) and is sometimes referred to as a weak base, or 'B_{TOT}' (in contrast to weak acids, A_{TOT}) [40].

$$THAM\text{-}NH_2 + H^+ \rightleftarrows THAM\text{-}NH_3^+ \quad \text{Eq. 4}$$

The positively charged protonated form of THAM can be quantitatively relevant and, in fact, increases the column of cations in the gamblegram (see Fig. 1). To ensure electrical neutrality, an equal amount of negative charges will be needed. These anions will derive from the dissociation of AH to A^- (Equation 2) and from the hydration of CO_2 to form HCO_3^- (Equation 3). For the latter aspect, and unlike sodium bicarbonate, THAM is CO_2 consuming and can therefore cause intracellular hypocapnic alkalosis [41]. Once protonated, THAM is excreted in the urine with either chloride or HCO_3^- as accompanying anions.

Table 5. Characteristics of blood components

	Fresh frozen plasma (n = 8)	Packed RBCs (n = 4)	Platelets (n = 5)
Na^+ (mEq L^{-1})	170 ± 1.4	119 ± 4	172 ± 1.8
K^+ (mEq L^{-1})	3.3 ± 0.2	45 ± 6	1.7 ± 0.1
Ca^{2+} (mEq L^{-1})[a]	7.1 ± 1.3	1.2 ± 0.2	3.3 ± 0.1
Mg^{2+} (mEq L^{-1})	1.2 ± 0.4	0.3 ± 0.1	0.6 ± 0.0
Cl^- (mEq L^{-1})	73 ± 2	100 ± 3	91 ± 1
Lactate (mEq L^{-1})	1.6 ± 0.5	25.8 ± 3.0	4.0 ± 0.4
Glucose (mEq L^{-1})	370 ± 11	323 ± 50	144 ± 6
Osmolarity (mOsm L^{-1})[b]	367 ± 3	346 ± 3	356 ± 4
Albumin (g L^{-1})	37 ± 2	0 ± 0[c]	14 ± 1
Phosphate (mg dL^{-1})	10.6 ± 0.3	13.3 ± 1.9	5.4 ± 0.2
Free Hb (g dL^{-1})	0 ± 0	0.07 ± 0.02	0 ± 0
SID (mEq L^{-1})	100.0 ± 1.7	38.3 ± 2.3	79.1 ± 1.2
Volume per unit (mL)	252 ± 18	300 ± 19	429 ± 21

Characteristics of blood components of our institution; $Ca2^+$ represents total calcium; free calcium is undetectable due to citrate addition; Osmolarity represents theoretical osmolarity calculated as ($Na^+ + K^+$) X 2 + Glucose, where Na^+ and K^+ are expressed in mEq L^{-1} and glucose in mmol L^{-1}; Albumin concentration in packed RBCs is below the detection limit of 5 g L^{-1}

BLOOD COMPONENTS

FRESH FROZEN PLASMA

Fresh frozen plasma (FFP) is characterised by high sodium (~170 mEq L^{-1}), low chloride (~70 mEq L^{-1}) and a consequent high SID (~100 mEq L^{-1}) [42]. Furthermore, FFP has an almost normal albumin concentration, a higher than normal phosphate concentration, and a calculated osmolarity of approximately 370 mOsm L^{-1} (Table 5).

These characteristics can be explained by the way blood components are processed. In our institution, whole blood (450 mL^{-1}) is collected in a bag containing citrate, phosphate and dextrose (CPD, 63 mL). Citrate is added in the form of trisodium citrate for its anticoagulant effect, phosphate as sodium dihydrogen phosphate as a buffer, to stabilise the solution's pH, and dextrose as a substrate for cellular metabolism. As sodium citrate does not enter red blood cells [43] most of the CPD solution is found in FFP, explaining the higher than normal sodium concentration and resulting in a theoretical citrate concentration of between 50 and 60 mEq L^{-1}. Chloride concentration is lower than normal, principally due to the dilution with chloride-free CPD.

Despite a probable increase in A_{TOT} caused by the infusion of an albumin containing phosphate-rich solution, the net effect on plasma acid-base equilibrium is a metabolic alkalosis due to the high SID of FFP, once citrate is metabolised [44].

PACKED RED BLOOD CELLS (RBCS)

Once the supernatant fraction of whole blood is removed, concentrated erythrocytes and buffy coat (platelets) are left over. In our institution, RBCs, once separated, are mixed with a 100 mL solution containing NaCl 0.9%, adenine, glucose and mannitol (SAGM) in order to increase their possible storage time. The resulting electrolyte composition is shown in Table 5. As can be noted, the sodium concentration of the extracellular volume is rather low (~120 mEq L^{-1}) despite the addition of 100 mL of 0.9% NaCl. On the other hand, potassium concentration is very high (~40 mEq L^{-1}).

This extremely unphysiological electrolyte composition is caused by a temperature-dependent reduced activity of the Na^+/K^+ pumps of red cell membranes [45], which results in an inward shift of sodium and an outward shift of potassium [46]. Indeed, packed RBCs are stored at 4°C. Also the lower than expected chloride concentrations (~100 mEq L^{-1}) can probably be explained by an electrolyte shift between extracellular and intracellular volume [47]. Finally, the high lactate concentration (~25 mEq L^{-1}) can be attributed to red cell metabolism. Of note, the degree of these electrolyte derangements is very variable and is correlated with storage time [46,48].

It is very likely that the electrolyte concentrations measured at 4°C (Table 5) differ significantly from the actual electrolyte composition once packed RBCs are heated to 37°C, i.e. once the Na^+/K^+ pump activity is restored. It is therefore quite difficult to predict plasma acid-base variations of packed RBCs transfusion basing the assumptions on electrolyte concentrations measured at storage temperature. For instance, a recent paper evaluated, in a cohort of critically ill patients, the acid-base effect of RBCs transfusions and found no change in pH and a slight increase in potassium, lactate and sodium [48]. Finally, it is worth underlining that, due to the high haematocrit of packed RBCs (~60%),

the amount of extracellular fluid is limited and the resulting dilutional effect on the patient's plasma is reduced.

PLATELETS

At our institution, platelet pools are derived from buffy coats of five donors which are subsequently diluted in 300 mL of a specific medium composed of sodium citrate, sodium acetate and sodium chloride. Similarly to FFP, the volume of platelet pools is almost completely extracellular and is composed of a mixture of plasma and preservation solution. The resulting solution has high sodium, low chloride and high SID (~80 mEq L^{-1}), once organic anions are metabolised by cellular metabolism (Table 5). Furthermore, the solution has a low concentration of albumin and phosphates, resulting in a low A_{TOT} concentration. Although direct experimental data is lacking, it is conceivable that the infusion of platelet pools induces a shift of plasma pH toward alkalosis. These effects are, however, rather theoretical, as the volume infused with platelet pools is usually very limited.

CONCLUSIONS AND CLINICAL RELEVANCE

Misinterpreting post-operative 0.9% NaCl-induced hyperchloremic acidosis for hypoperfusion and hypovolemia could have the straightforward drawback of additional fluid therapy with potential fluid overload, therefore adding iatrogenic harm to the acidosis which is already caused by medical intervention. This simple example underlines the importance of (i) choosing the right intravenous fluid and (ii) being aware of acid-base derangements induced by intravenous fluid therapy. Indeed, knowledge of the composition of the intravenous fluids we prescribe is fundamental, similarly to every other type of intravenous drug. The combination of this information with the application of simple physicochemical rules best described by Stewart's approach is crucial to understanding and predicting changes of acid-base equilibrium induced by fluid therapy, reducing the risk of iatrogenic acid-base derangements.

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