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J Intensive Care Med 2010 25: 271 originally published online 10 July 2010

DOI: 10.1177/0885066610371633

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Journal of Intensive Care Medicine
25(5) 271-280
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DOI: 10.1177/0885066610371633
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Abstract

The objective of this study is to develop a physicochemical model of the projected change in standard base excess (SBE) consequent to the infused volume of crystalloid solutions in common use. A clinical simulation of modeled acid-base and fluid compartment parameters was conducted in a 70-kg test participant at standard physiologic state: pH = 7.40, partial pressure of carbon dioxide (PCO₂) = 40 mm Hg, Henderson–Hasselbalch actual bicarbonate ([HCO₃]_{HH}) = 24.5 mEq/L, strong ion difference (SID) = 38.9 mEq/L, albumin = 4.40 g/dL, inorganic phosphate = 1.16 mmol/L, citrate total = 0.135 mmol/L, and SBE = 0.1 mEq/L. Simulations of multiple, sequential crystalloid infusions up to 10 L were conducted of normal saline (SID = 0), lactated Ringer's (SID = 28), plasmalyte 148 (SID = 50), one-half normal saline + 75 mEq/L sodium bicarbonate (NaHCO₃; SID = 75), 0.15 mol/L NaHCO₃ (SID = 150), and a hypothetical crystalloid solution whose SID = 24.5 mEq/L, respectively. Simulations were based on theoretical completion of steady-state equilibrium and PCO₂ was fixed at 40 mm Hg to assess nonrespiratory acid-base effects. A crystalloid SID equivalent to standard state actual bicarbonate (24.5 mEq/L) results in a neutral metabolic acid-base status for infusions up to 10 L. The 5 study solutions exhibited curvilinear relationships between SBE and crystalloid infusion volume in liters. Solutions whose SID was greater than 24.5 mEq/L demonstrated a progressive metabolic alkalosis and less, a progressive metabolic acidosis. In a human model system, the effects of crystalloid infusion on SBE are a function of the crystalloid and plasma SID, volume infused, and nonvolatile plasma weak acid changes. A projection of the impact of a unit volume of various isotonic crystalloid solutions on SBE is presented. The model's validation, applications, and limitations are examined.

Keywords

crystalloid resuscitation, strong ion difference, acid-base status, standard base excess, metabolic acidosis, metabolic alkalosis

Received March 23, 2009, and in revised form July 22, 2009. Accepted September 8, 2009.

Introduction

Large volume crystalloid resuscitation in hypovolemic shock remains a cardinal maneuver to restore adequate tissue perfusion and oxygen delivery. Traditionally, the fluid resuscitation strategy is directed by goal-directed hemodynamic and clinical endpoints and fails to link the physicochemical properties of the infusate crystalloid solution or crystalloid strong ion difference (SID).^{1,2} The crystalloid SID is the net electrical charge difference of the infusate strong cations minus the anions. Strong ions (Na⁺, K⁺, Mg²⁺, Ca²⁺, Cl⁻, and lactate) remain fully ionized at physiologic pH. Normal saline, for example, contains 154 mEq/L of sodium and 154 mEq/L of chloride and, thus, the SID is equal to zero.

The clinical consequences of large volume crystalloid infusion on the acid-base status of the critically ill recipient are often disregarded in the current published literature on prescriptions for fluid resuscitation in acute illness.^{3,4} Normal saline remains a preferred resuscitation fluid by many clinicians irrespective of the patient's initial base deficit, serum chloride

level, or high likelihood of developing a complicating hyperchloremic metabolic acidosis.⁵ Saline-related infusion acidosis does not appear to have any significant detrimental effects on outcome in patients with normal acid-base status and renal function at the outset of major surgery.⁶⁻⁸ In critical illness with multiorgan dysfunction and an evolving metabolic acidosis, the question of potential harm remains uncertain but suspected.⁹⁻¹¹ A rational basis for understanding the effects of crystalloid

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Table 1. Standard Physiological State in Plasma for Test Participant (Total Body Water Equal to 55% Total Body Weight)

pH-Regulating Variables				Derived Parameters		
SID (mEq/L)	38.9	Weight (Kg)	70.0	pH	7.400	
PCO ₂ (mm Hg)	40.0	TBW (L)	38.5	[HCO ₃] _{H+H} (mEq/L)	24.5	
A _{tot}		ECV (L)	12.8	SBE (mEq/L)	0.1	
Albumin (g/dL)	4.40	PV (L)	3.2			
Phosphate (mmol/L)	1.16					
Citrate total (mmol/L)	0.135					

Abbreviations: A_{tot}, plasma nonvolatile weak acid buffer content; ECV, extracellular compartment volume; [HCO₃]_{H+H}, Henderson–Hasselbalch actual bicarbonate; PCO₂, partial pressure of carbon dioxide; PV, plasma volume; SID, strong ion difference; SBE, standard base excess; TBW, total body water.

Table 2. Isotonic Crystalloid Solutions^a

Crystalloid Solution	[Na ⁺]	[Cl ⁻]	[K ⁺]	[Ca ²⁺]	Lactate	Acetate	Gluconate	[Mg ²⁺]	SID	Osmolality
0.9% NS	154	154	0	0	0	0	0	0	0	308
Ringer's lactate	130	109	4	3	28	0	0	0	28	275
Plasmalyte 148	140	98	5	0	0	27	23	3	50	294
1/2 NS with 75 mEq/L NaHCO ₃	152	77	0	0	0	0	0	0	75	304
0.15 mol/L NaHCO ₃	150	0	0	0	0	0	0	0	150	300

Abbreviations: [Na⁺], sodium; [Cl⁻], chloride; [K⁺], potassium; [Ca²⁺], calcium; [Mg²⁺], magnesium; SID, strong ion difference; NS, normal saline; NaHCO₃, sodium bicarbonate.

^a All electrolyte ions are expressed in mEq/L.

infusion on acid-base has been unavailable until recently and consequently clinical studies examining the effects of different crystalloid solutions on benefit, morbidity, and outcome may have been underpowered and poorly designed.¹²

Stewart's physicochemical model of *in vivo* plasma metabolic acid-base status theoretically explains the differential effect of crystalloid infusion on plasma metabolic acid-base status.¹³ *In vivo* plasma pH is a function of 3 independent determinants: (1) SID; (2) nonvolatile weak acid concentration (A_{tot}); and (3) partial pressure of carbon dioxide (PCO₂). Infusion of an isotonic crystalloid solution modifies plasma pH by simultaneously altering 2 of the 3 independent determinants. For example, normal plasma SID equals 38.9 mEq/L and when combined with a zero SID crystalloid infusate (normal saline) will reduce plasma SID by admixture, resulting in a strong ion acidosis. Crystalloid solutions are devoid of A_{tot} (albumin, inorganic phosphate, and total citrate) and intravenous administration will reduce plasma weak acids by simple dilution, resulting in a mitigating dilution alkalosis.¹⁴

The injury response of critical illness also affects A_{tot} by its effects on serum albumin, increased catabolism and reduced synthesis, reduction from hemorrhage and/or exudative losses, and increased capillary permeability clinically recognized as the degree of hypoalbuminemia.¹⁵ Metabolic acid-base status measured as standard base excess (SBE) is a summation function of the changes in both plasma SID and A_{tot}.¹⁶

Standard base excess remains a useful clinical tool in the intensive care unit.¹⁷ It is easily calculated by an arterial blood gas measurement and reduces metabolic acid-base disturbances to a simple, quantitative numerical scale. Standard base excess provides no insight into mechanism but provides the magnitude

and direction of a metabolic acid-base disturbance. A positive value indicates an excess of base, whereas a negative value indicates an excess of fixed acid *in vivo* with respect to the extracellular fluid compartment.

The objective of this study is to develop a human physicochemical model of the change in SBE consequent to the infused volume of commonly used crystalloid solutions. This simulation is intended to provide a conceptual framework for understanding the physicochemical consequences of high volume isotonic crystalloid infusion on plasma metabolic acid-base status. A human physicochemical model of crystalloid infusion would provide an alternative paradigm for designing clinical studies to determine crystalloid infusion-related benefit, morbidity, and outcome. The model's validation, applications, and limitations are examined.

Materials and Methods

The objective of this study was to quantitatively model the projected change in SBE in a 70-kg test participant at standard physiologic state (Table 1) in response to multiple, sequential crystalloid infusion experiments up to 10 L of normal saline (0.9%), lactated Ringer's, plasmalyte 148, one-half normal saline with 75 mEq/L sodium bicarbonate (NaHCO₃), and 0.15 mol/L NaHCO₃ solutions, respectively (Table 2). The crystalloid solutions represent a spectrum of SID values from 0 to 150 mEq/L.

Experimental *in vitro* and *in vivo* studies suggest that a crystalloid SID that approximates plasma bicarbonate concentration should result in neutral metabolic acid-base status after volume infusion.^{18,19} This hypothesis was quantitatively

modeled by a hypothetical crystalloid solution $SID = 24.5 \text{ mEq/L}$ which is equivalent to standard state bicarbonate concentration.

In the Figge-Fencel Quantitative Physicochemical Model, there are 3 independent determinants of plasma hydrogen and bicarbonate ion concentration in vivo: PCO_2 , SID , and A_{tot} (albumin, inorganic phosphorus, and total citrate).²⁰⁻²² The PCO_2 was fixed at 40 mm Hg to assess nonrespiratory acid-base effects. The model simulation was focused on the change in A_{tot} (mmol/L) consequent to simple dilution of the nonvolatile weak acid buffers. A decrease in A_{tot} is equivalent to a gain in plasma base or a metabolic alkalosis.

Crystalloid infusion changes the body fluid compartment volumes, which in turn changes the concentrations of the plasma strong ions and SID . Standard state body fluid compartment parameters were set as follows: total body water was equal to 55% total body weight with 33.3% total body water equal to extracellular compartment volume. Plasma volume was defined as 25% of extracellular volume according to convention.²³

Crystalloid infusion changes plasma SID by changing the proportion of strong cations to strong anions and, thus, the net charge balance. After crystalloid infusion, plasma SID_{ad} (admixture) reflects the admixture of the crystalloid SID and plasma SID . The major strong cations and anions will also be diluted by the increment in plasma volume by the infusate. The plasma SID_{ad} from standard state conditions is calculated as follows: SID_{ss} (standard state) \times plasma volume + SID_{ci} (crystalloid infusate) \times infusate volume divided by plasma volume + infusate volume. The plasma SID_{ad} calculation after a 1 L infusion of normal saline from standard state can be found in the appendix.

New steady-state parameters were calculated after each infusion experiment to deduce the increment or decrement in plasma SID_{ad} (Appendix A) and A_{tot} (Appendix B), which allowed calculation of the pH by the Figge-Fencel quantitative physicochemical model (Appendix C). The Figge-Fencel model was solved by an iterative computer program adapted to Microsoft Excel Visual Basic for Applications 2003 (Microsoft, Redmond, Washington) and is available online at <http://www.figge-fencel.org/>. The model can be used to calculate the pH of plasma for any set of values for PCO_2 , SID , and A_{tot} . The pH was iteratively solved for each dilution experiment, which allowed calculation of the actual bicarbonate and SBE (Appendix D and E).

Linear and second-degree polynomial regressions of the SBE on infusion volumes, up to 10 L for each crystalloid solution, were calculated by Analyze-it statistical software package (Analyze-It Software, Ltd, Leeds, England, UK). Descriptive statistics and formula calculations were performed using Microsoft Excel 2003 Data Analysis Package (Microsoft, Redmond, Washington).

The first assumption in the physicochemical simulation model is that the only variable disturbing the body's content of water and strong ions during infusion is the administered crystalloid infusate. The second assumption is instantaneous completion of steady-state equilibrium after crystalloid

infusion with complete and homogenous mixing in the apparent volumes of distribution of sodium and chloride. Normally, this may take 1 to 2 hours as fluid and electrolytes move between body compartments.^{24,25} The third assumption is that the Gibbs-Donnan equilibrium does not influence the distribution of strong ions between the interstitial and intravascular compartments.²⁶ The final assumption is that A_{tot} is not altered by the injury response from acute illness. Isotonic solutions were chosen because no significant osmotic disturbance is generated between the extracellular and intracellular fluid compartments.

Results

The effects of crystalloid infusion on SBE are a function of the crystalloid and plasma SID , volume infused, and A_{tot} changes (Figure 1 and Table 3). A crystalloid SID ($SID = 24.5 \text{ mEq/L}$) equivalent to standard state actual bicarbonate (24.5 mEq/L) results in a neutral metabolic acid-base status or $SBE \approx 0 \text{ mEq/L}$ for infusions up to 10 L. Linear regression of SBE against crystalloid infusion volume (CIV) was predicted by $SBE = -0.0218 \times CIV + 0.0714$ ($R^2 = .9206$).

The larger the infused volume, the greater the displacement of SBE from 0 mEq/L when crystalloid SID and actual bicarbonate are discordant. The lower the crystalloid SID relative to actual bicarbonate, the greater the standard base deficit; the greater the crystalloid SID relative to actual bicarbonate, the greater the SBE.

Normal saline infusions from standard physiological state yield a negative curvilinear relationship with SBE. Second degree polynomial regression of SBE against CIV was predicted by $SBE = 0.0578 \times CIV^2 - 1.7877 \times CIV - 0.0841$ ($R^2 = .9997$). A 1-L infusion results in metabolic acidosis and an $SBE = -1.8 \text{ mEq/L}$.

Ringer's lactate infusions from standard physiological state yield a positive curvilinear relationship with SBE. Second-degree polynomial regression of SBE against CIV was predicted by $SBE = -0.0084 \times CIV^2 + 0.2447 \times CIV + 0.1223$ ($R^2 = .9977$). A 1-L infusion results in a metabolic alkalosis and $SBE = 0.4 \text{ mEq/L}$.

Plasmalyte 148 infusions from standard physiological state yield a positive curvilinear relationship with SBE. Second-degree polynomial regression of SBE against CIV was predicted by $SBE = -0.0668 \times CIV^2 + 1.8347 \times CIV + 0.2659$ ($R^2 = .9996$). A 1-L infusion results in a metabolic alkalosis and an $SBE = 2.1 \text{ mEq/L}$.

One-half normal saline with 75 mEq/L $NaHCO_3$ infusions from standard physiological state yield a positive curvilinear relationship with SBE. Second-degree polynomial regression of SBE against CIV was predicted by $SBE = -0.131 \times CIV^2 + 3.5773 \times CIV + 0.5089$ ($R^2 = .9994$). A 1-L infusion results in a metabolic alkalosis and an $SBE = 4.0 \text{ mEq/L}$.

Sodium bicarbonate (0.15 mol/L) infusions from standard physiological state yield a positive curvilinear relationship with SBE. Second-degree polynomial regression of SBE against CIV was predicted by $SBE = -0.5098 \times CIV^2 + 9.7416 \times$

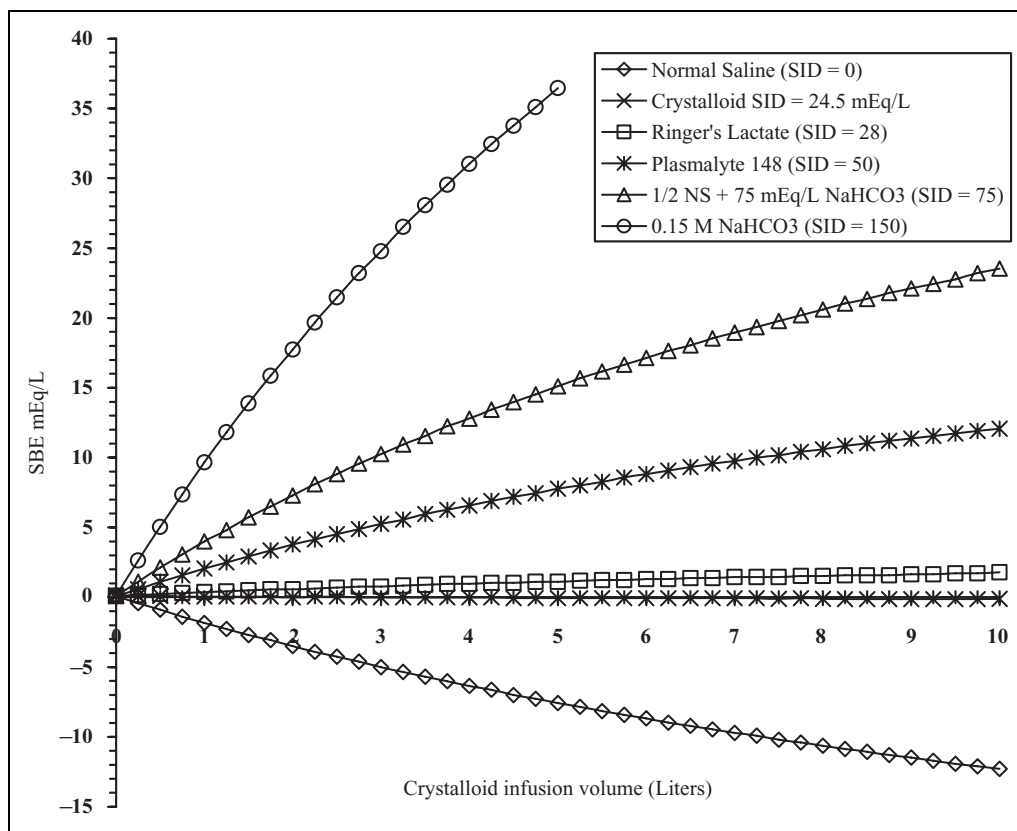


Figure 1. Standard base excess (SBE) as a function of crystalloid infusion volume in liters.

Table 3. Physicochemical Consequences of a 1 L Crystalloid Infusion From Standard State Stratified by Changes in SID, pH, and SBE

	NS SID = 0	SID = 24.5	LR SID = 28	Standard State SID = 38.9	Plasmalyte SID = 50	1/2 NS + 75 mEq/L NaHCO ₃ SID = 75	0.15 mol/L NaHCO ₃ SID = 150
SID (mEq/L)	36.1	37.8	38.1	38.9	39.7	41.5	46.9
pH	7.370	7.400	7.404	7.400	7.429	7.456	7.528
PCO ₂ (mm Hg)	40	40	40	40	40	40	40
[HCO ₃] _{H-H} mEq/L	22.9	24.5	24.7	24.5	26.2	27.9	32.9
SBE (mEq/L)	-1.8	0.1	0.4	0.1	2.1	4.0	9.7

Abbreviations: NS, normal saline; LR, lactated Ringer's; NaHCO₃, sodium bicarbonate; SID, strong ion difference; SBE, standard base excess; [HCO₃]_{H-H}, Henderson-Hasselbalch actual bicarbonate; PCO₂, partial pressure of carbon dioxide.

CIV + 0.2931 ($R^2 = .9999$). A 1-L infusion results in a metabolic alkalosis and an SBE = 9.7 mEq/L.

Model Validation

Acute normovolemic hemodilution studies, both in vitro and in vivo, support the physicochemical model. Morgan et al¹⁸ performed serial dilutions of fresh blood with in vitro crystalloid SID solutions ranging from -4 mEq/L to 40 mEq/L. Plasma SID and whole blood base excess were linearly related to diluent crystalloid SID. In addition, when plasma SID was held constant after hemodilution with a balanced crystalloid, the decrement in A_{Tot} correlated with the development of a metabolic alkalosis.

The study concluded that neutral metabolic acid-base status after dilution would require a crystalloid SID equal to 24 mEq/L. Crystalloid SID solutions less than and greater than 24 mEq/L caused metabolic acidosis and alkalosis, respectively.

Morgan et al¹⁹ followed with a prospective in vivo study of acute, progressive normovolemic hemodilution in a Sprague-Dawley rat model. In all, 7 diluent crystalloid SID solutions ranging from 0 to 40 mEq/L were administered. A linear relationship between crystalloid SID and SBE was demonstrated. Crystalloid SID solutions less than and greater than 24 mEq/L caused metabolic acidosis and alkalosis, respectively. Linear regression analysis of SBE versus crystalloid SID demonstrated that neutral metabolic acid-base status (SBE = 0 mEq/L) after

Table 4. Comparison of Normal Saline (0.9%) Infusion: Actual Versus Predicted Model Parameters From Standard State

	Scheingraber et al	Predicted Model Parameters	Rehm et al (THAM group)	Predicted Model Parameters	Rehm et al (BIC group)	Predicted Model Parameters	Bruegger et al	Predicted Model Parameters
Mean volume infused (L)	4.080		5.183		5.342		5.744	
Weight (kg)	68	70	66	70	66	70	71	70
Final pH	7.280	7.291	7.280	7.267	7.278	7.259	7.284	7.254
Final PaCO ₂ (mm Hg)	40	40	40.4	40	40.6	40	37.5	40
Final [HCO ₃] _{H-H} (mEq/L)	18.4	19.1	18.4	18.0	18.4	17.7	18.1	17.5
SID (mEq/L)	30	29.5	28.6	27.7	28.5	27.5	28.7	26.9
Total protein (g/dL)	4.3	5.8	NA	5.5	NA	5.4	4.3	5.3
SBE (mEq/L) derived	-7.2	-6.5	-7.2	-7.7	-7.3	-8.2	-7.4	-8.4

Abbreviations: [HCO₃]_{H-H}, Henderson–Hasselbalch actual bicarbonate; PCO₂, partial pressure of carbon dioxide; THAM, Tris-Hydroxymethyl Aminoethane; BIC, Sodium Bicarbonate.

dilution requires a crystalloid SID = 24.4 mEq/L, which is equal to standard state plasma bicarbonate concentration. The authors' concluded that given the similarities of rat and human blood, the results could be extrapolated to human participants.

The human physicochemical model's predictions were compared with high-quality experimental data in the published literature for normal saline, lactated Ringer's, and plasmalyte solutions, respectively (Tables 4-6).^{7,27-29} Model predictions were calculated from standard physiological state and were not corrected for differences in weight or baseline acid-base status. The clinical studies by Scheingraber et al⁷ and Bruegger et al²⁸ were conducted with a lactated Ringer's solution crystalloid SID = 27 mEq/L not 28 mEq/L, which is the current formulation (Table 5). The model was adjusted for this discrepancy. The pH, SBE, and [HCO₃] actual and predicted data sets accord well.

No observational or prospective human studies were found in PubMed regarding one-half normal saline with 75 mEq/L NaHCO₃ or isotonic 0.15 mol/L NaHCO₃. The solutions are in common use at the authors' institutions and are presented for discussion purposes only.

Discussion

The clinical basis for this study is to develop a physicochemical model of high-volume crystalloid infusion on acid-base status. Theoretically, selective crystalloid infusion can manipulate the SBE in a predictable and quantitative manner. The authors' intent is to develop a framework for clinical research studies that simultaneously maximize goal-directed hemodynamic endpoints and minimize crystalloid-induced or pathologic metabolic acid-base disturbances in the acute resuscitative phase of critical illness. A physicochemical resuscitation strategy is physiologically appealing but untested.

The physicochemical model presented is simplistic but conceptually instructive. A similar model has been proposed by

Constable.³⁰ The complex interplay of plasma strong ions and crystalloid SID formed the cornerstone of acid-base analysis and fluid replacement therapy in the beginning to mid-twentieth century.³¹ The early physician scientists attempted to not only correct the fluid deficit but also the metabolic acid-base derangement by restoring the normal amounts and concentrations of the extracellular strong ions, a prescient and noble goal at the time.

The hypothesis that crystalloid SID affects plasma metabolic acid-base status in a logical and consistent manner was first proposed and then reviewed by Morgan.^{12,32} The *in vivo* determinants of plasma metabolic acid-base status are SID, PCO₂, and A_{tot}. The volume of distribution of the major crystalloid strong ions is the extracellular fluid compartment. Crystalloid infusion forces the plasma SID toward the crystalloid SID by admixture. Crystalloid solutions are devoid of A_{tot} and infusion will result in simple dilution, resulting in a metabolic alkalosis. Plasma metabolic acid-base status will be determined after equilibration and Gibbs-Donnan effect by the plasma SID admixture and diluted A_{tot}.

If the induced crystalloid strong ion acidosis is exactly balanced by a dilution A_{tot} metabolic alkalosis, no significant change in SBE occurs. The crystalloid SID necessary to achieve this "balance point" was experimentally determined to be 24 mEq/L or equivalent to the preinfusion actual bicarbonate concentration. The physicochemical model demonstrates this phenomenon when crystalloid SID is set to standard state actual bicarbonate (24.5 mEq/L) for up to 10 L. The small difference between the experimental and theoretical value is likely secondary to differences in standard state prior to infusion.

The "balance point" has remarkable use in the design of fluids to achieve a particular acid-base endpoint. If the infused crystalloid SID is greater than 24.5 mEq/L, metabolic alkalosis will result; if less than 24.5 mEq/L, metabolic acidosis will

Table 5. Comparison of Lactated Ringer's Infusion: Actual Versus Predicted Model Parameters From Standard State

	Scheingraber et al	Predicted Model Parameters	Breugger et al	Predicted Model Parameters
Mean Volume Infused (L)	4.620		5.456	
Weight (kg)	77	70	81	70
Final pH	7.400	7.411	7.422	7.412
Final PCO ₂ (mm Hg)	40	40	38	40
Final [HCO ₃] _{HH} (mEq/L)	23.0	25.1	24.4	25.2
Final SID (mEq/L)	33.8	35.8	33.7	35.4
Total protein (g/dL)	4.3	5.7	4.2	5.4
SBE (mEq/L) derived	-1.3	0.8	0.3	0.9

Abbreviations: [HCO₃]_{HH}, Henderson–Hasselbalch actual bicarbonate; PCO₂, partial pressure of carbon dioxide; SBE, standard base excess; SID, strong ion difference.

Table 6. Comparison of Plasmalyte Infusion: Actual Versus Predicted Model Parameters From Standard State

	Liskaser et al (Group 2)	Predicted Model Parameters
Mean volume infused (L)	1.500	
Weight (kg)	NA	70
Final pH	7.440	7.441
Final PCO ₂ (mm Hg)	39.5	40
Final [HCO ₃] _{HH} (mEq/L)	25.9	26.9
Final SID (mEq/L)	34.4	40.1
Albumin (g/dL)	2.4	3.9
SBE (mEq/L) derived	1.9	2.9

Abbreviations: [HCO₃]_{HH}, Henderson–Hasselbalch actual bicarbonate; PCO₂, partial pressure of carbon dioxide; SBE, standard base excess; SID, strong ion difference.

result (Figure 1). The model demonstrates the potency of various crystalloid solutions as a function of crystalloid SID to induce an acidosis or alkalosis, respectively, from standard-state conditions.

Crystalloid solutions with an ionic composition similar to plasma and SID close to standard state bicarbonate are referred to as balanced solutions (lactated Ringer's and Hartmann's solution) and clinically minimize acid-base disturbances when infused. The model, for example, predicts a mild metabolic alkalosis after lactated Ringer's infusion from standard state.

The potential exists for aggravating a preexisting metabolic acid-base derangement with imprudent choice of crystalloid (Figure 2). For example, normal saline (0.9%) infusion (SID = 0 mEq/L) would aggravate a metabolic acidosis (SBE ≤ -5 mEq/L) by inducing a coexisting hyperchloremic strong ion acidosis. Saline-induced hyperchloremic acidosis is well recognized in the literature and may be potentially harmful.^{9,33,34}

An unexpected finding was that the crystalloid SID "balance point" was different in metabolic acidosis than in standard physiological state (Figure 2). For example, if pH = 7.312, PCO₂ = 40 mm Hg, Henderson–Hasselbalch actual bicarbonate ([HCO₃]_{HH}) = 20.0 mEq/L, SBE = -5.3 mEq/L, SID = 33.9 mEq/L, and lactic acid = 5 mmol/L, a balanced crystalloid solution would have to equal 20 mEq/L to prevent changes in

SBE. In this example, crystalloid SID must be equal to the preinfusion actual bicarbonate concentration and not standard state bicarbonate concentration (24.5 mEq/L) to maintain a constant SBE with high volume infusion.

The authors' hypothesized that the infusate crystalloid SID must equal preinfusion actual bicarbonate to prevent infusion-related acid-base abnormalities. To test this hypothesis, the physicochemical model was run with preinfusion parameters as follows: plasma SID was varied from 15 to 55 mEq/L, PCO₂ = 40 mm Hg, A_{tot} was clamped to standard state (albumin = 4.4 g/dL, P_I = 1.16 mmol/L, citrate total = 0.135 mmol/L). The pH was varied between 6.713 and 7.606, bicarbonate range 5.037 to 39.373 mEq/L, resulting in an SBE range -27.44 to 16.74 mEq/L. The preinfusion pH, bicarbonate, and SBE were calculated and the crystalloid SID was set to preinfusion bicarbonate. The model was run for 5 L crystalloid infusions. Linear regression of postinfusion SBE against preinfusion SBE was predicted by post-SBE = 1.0003 × preinfusion-SBE ($R^2 = 1$). The graph is essentially a line of identity suggesting that this modeled relationship holds true for physiologic strong ion acidosis and alkalosis, and standard state conditions (Figure 3). This relationship allows quick determination of the crystalloid SID "balance point," which would be equal to the preinfusion actual bicarbonate concentration. This hypothesis is without experimental support at this time but merits additional investigation.

In moderate-to-severe metabolic acidosis, a more rational strategy would be to use lactated Ringer's solution, which would minimize crystalloid strong ion acidosis. Several animal studies have demonstrated a mortality benefit with this approach.^{35,36} The crystalloid SID of lactated Ringer's (SID = 28 mEq/L) assumes rapid and complete metabolism of the lactate component, resulting in bicarbonate replacement and a mild metabolic alkalosis. However, when infused against a lactic acidosis, the in vivo effective SID of lactated Ringer's would be theoretically reduced by the serum concentration of lactate because it is not subject to metabolic disappearance (unless the microcirculatory abnormality is corrected by infusion). For example, when serum lactate is equal to 5 mmol/L, the crystalloid SID of lactated Ringer's solution would be reduced to 23 mEq/L but would still generate a mild metabolic

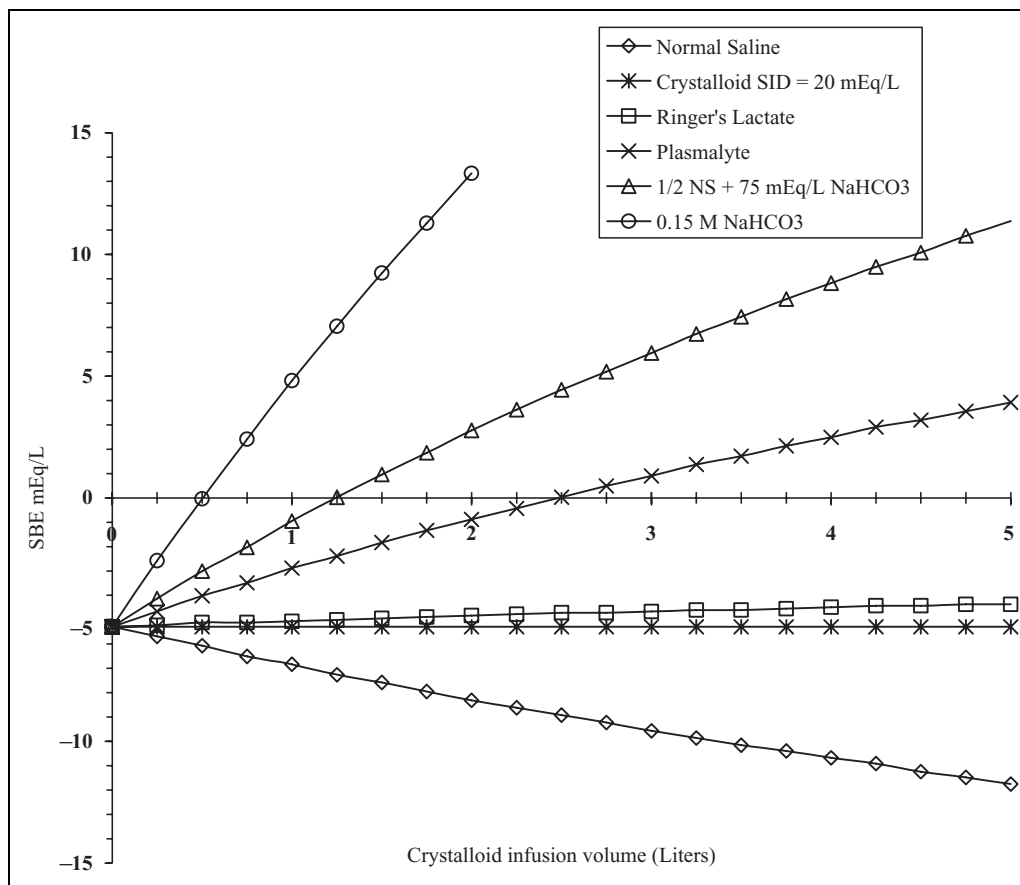


Figure 2. Crystalloid infusion during moderately severe metabolic acidosis: pH = 7.312, PCO₂ = 40 mm Hg, [HCO₃]_{HH} = 20.0 mEq/L, SBE = -5.3 mEq/L, SID = 33.9 mEq/L, lactate = 5 mmol/L. SBE indicates standard base excess; SID, strong ion difference.

alkalosis because of the reduction in the crystalloid SID “balance point” to 20 mEq/L (Figure 2).

In practice, incomplete metabolism of the lactate component of lactated Ringer’s solution is thought to occur. Lactated Ringer’s solution consists of a racemic mixture of D(-) and L(+) stereoisomers where the L(+) isomer predominates. The L(+) isomer is rapidly metabolized to pyruvate but the D(-) isomer is thought to have a slower elimination route and may accumulate in the blood. Consequently, the effective SID of lactated Ringer’s is likely closer to 24.5 mEq/L, resulting in a neutral metabolic acid-base status after infusion from standard state conditions.^{37,38} This phenomenon is demonstrated in the studies by Scheingraber⁷ and Bruegger.²⁸

Balanced resuscitation solutions, however, do not restore SBE to standard state conditions when preexisting moderate-to-severe metabolic acidosis prevails. In metabolic acidosis, the greater the crystalloid SID relative to actual bicarbonate, the greater the SBE change or alkalinizing effect. An alternative resuscitation strategy would be to use an isotonic crystalloid whose SID is far greater than preinfusion actual bicarbonate. Figure 2 demonstrates that 500 mL of 0.15 mol/L NaHCO₃ (SID = 150 mEq/L), 1250 mL of one-half normal saline + 75 mEq/L NaHCO₃ (SID = 75 mEq/L), or 2500 mL of plasmalyte 148 (SID = 50 mEq/L) would move SBE toward standard state and be corrective. Physicochemical resuscitation is distinctly

different from previous alkalization strategies, which were historically hypertonic, hyperosmolar (0.7-0.9 mol/L, SID = 700-900 mEq/L), and without a physicochemical endpoint.^{39,40} Isotonic and hypotonic alkalization strategies are in common use. Their clinical use remains limited secondary to the lack of defined endpoints of resuscitation and the absence of supportive prospective, randomized clinical studies in hypovolemic shock.

The treatment of hypovolemic shock is guided by a resuscitation strategy that restores standard physiologic state by goal-directed hemodynamic and microcirculatory endpoints. The relevant clinical questions regarding volume resuscitation are the type of crystalloid solution, the volume and velocity of infusion, and the relevant therapeutic endpoints.⁴¹⁻⁴³ The optimal fluid resuscitation strategy remains controversial and is currently unknown. The physicochemical fluid replacement model presented provides guidance on the type of crystalloid solution, volume infused, and endpoint of resuscitation. The data required for this analysis are available from arterial blood gases (pH, PCO₂, SBE, [alb], [P_i]) and serum chemistry profiles (Na⁺, K⁺, Ca²⁺, Mg²⁺, Cl⁻).

Conceptually, at the outset of resuscitation, an infusate crystalloid SID would be chosen to restore metabolic acid-base status toward standard state guided by SBE. The volume and velocity of infusion would be dictated by hemodynamic and microcirculatory endpoints. The infusate crystalloid SID would be serially

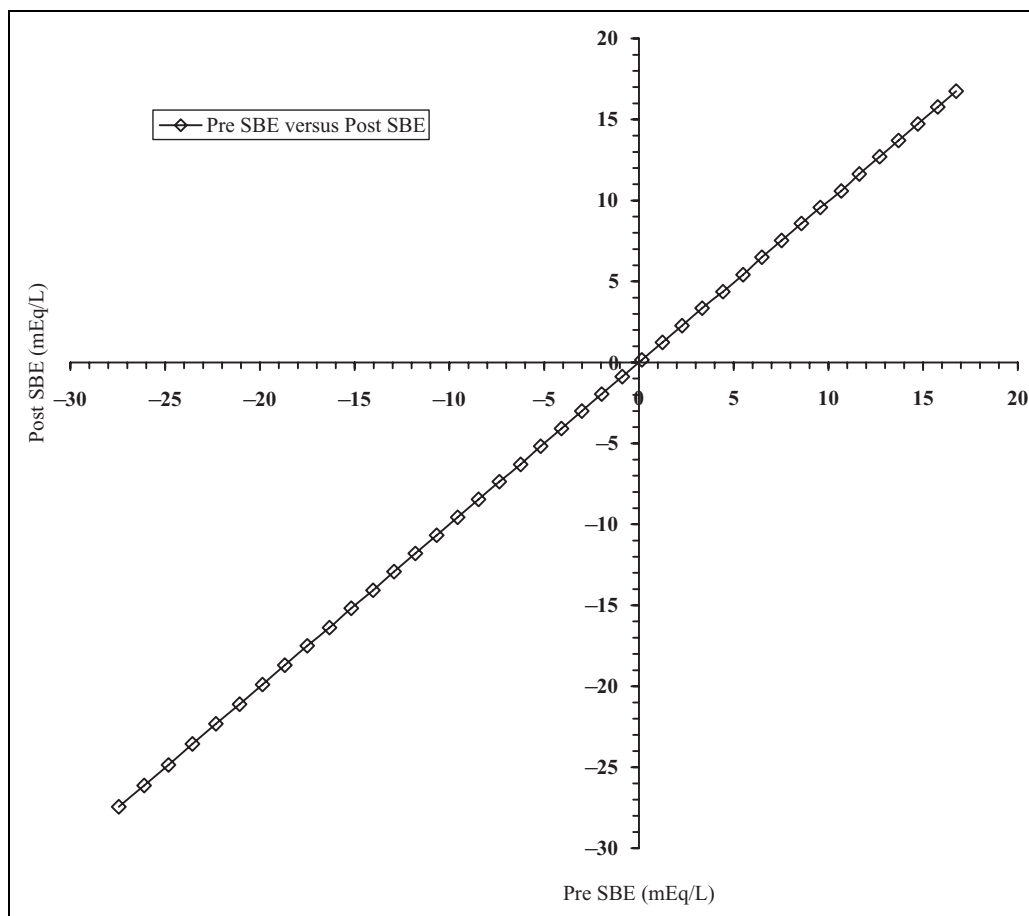


Figure 3. Predicted postinfusion SBE as a function of preinfusion SBE after 5 L infusions of crystalloid SID equal to preinfusion bicarbonate concentration. The physicochemical model was run for plasma SID (15-55 mEq/L), PCO_2 and A_{tot} were clamped to standard state. If crystalloid SID is equal to preinfusion actual bicarbonate, preinfusion SBE and postinfusion SBE form a line of identity. SBE indicates standard base excess; SID, strong ion difference.

adjusted based on reassessment of the plasma SID, arterial PCO_2 , A_{tot} , and SBE. Serial reassessment would be necessary to account for changes in PCO_2 in mechanically ventilated patients; physicochemical buffering and the Gibbs-Donnan equilibrium that would alter the plasma SID; and A_{tot} changes from hemorrhage, exudative losses, or increased capillary permeability. Once a neutral or targeted acid-base status has been achieved, acute resuscitation may proceed with a balanced solution to prevent further crystalloid-induced acid-base disturbances.

The physicochemical resuscitation model presented projects the effects of crystalloid infusion on acid-base status from standard state under ideal conditions. This was done primarily as a heuristic tool to demonstrate the dynamic effects of crystalloid SID on plasma acid-base status. The question remains whether the model “behaves well” when real data are applied. The acid-base effects of crystalloid infusion can be projected from any initial physiologic state where in vivo crystalloid SID, arterial PCO_2 , plasma SID, and A_{tot} are defined with a simple computer program. This is demonstrated in Tables 4 through 6 and theoretically in Figure 2. The Scheingraber⁷ and Liskaser²⁹ studies are considered as the most accurate and complete data sets available. The model’s projections are reasonably accurate

in these noncritically ill surgical patient populations during perioperative fluid replacement. High-quality clinical data sets are unfortunately lacking. No data sets are available in critically ill populations.

The model’s steady state assumption and simplifications limit direct extension to critical illness and merit careful scrutiny. Error is introduced into the model’s projections of acid-base status primarily by fluid, protein, and ion shifts between the vascular and interstitial compartments; and fluid, protein, and ion losses during the highly perturbed state of critical illness. Changes in these parameters are exceedingly difficult to predict or model. In the Figge-Fencel Quantitative Physicochemical Model, $pH = f_{pH}(PCO_2, SID, [alb], [P_i], [citrate])$ and has been validated in critical care populations.²⁰⁻²² The Figge-Fencel model is an integral part of the current model’s formulation and functions as an anchor for correction of the acid-base projection by serial reassessment of the of 3 independent determinants of plasma hydrogen ion concentration (SID, PCO_2 , and A_{tot}) in vivo. The proposed model is an approximation at best but may be useful in the design of future studies on the effects of crystalloid infusion on acid-base status and clinical outcome.

A proactive, physicochemical resuscitation strategy is conjecture at this time but is conceptually appealing from a physiologic point of view. Restoring homeostasis and standard state conditions early in critical illness may have benefits that transcend simple correction of acid-base status. The value of this strategy in critically ill patients is unknown and has not yet been studied. Whether correction of acid-base status by physicochemical principles in the acute resuscitative phase of critical illness results in improved patient outcome remains to be determined and merits continued clinical dialogue and research.

Appendix

- A. SID_{ad} (1 L normal saline infusion) =
 $(SID_{ss} [38.90 \text{ mEq/L}] \times \text{plasma volume} (3.21 \text{ L}) +$
 $SID_{ci} (0 \text{ mEq/L}) \times$
 increment in plasma volume $(0.25 \text{ L}) / \text{new plasma volume} (3.21 \text{ L} +$
 $0.25 \text{ L}) = 36.09 \text{ mEq/L}$
- B. Derived change in A_{tot} (1 L normal saline infusion) =
1. Total body water = $70.00 \text{ kg} \times 0.55 = 38.50 \text{ L}$
 2. Extracellular compartment volume = $38.50 \text{ L} \times 0.33 = 12.82 \text{ L}$
 3. Plasma volume = $12.82 \text{ L} \times 0.25 = 3.21 \text{ L}$
 4. Extracellular compartment volume after 1 L normal saline = $12.82 \text{ L} + 1.00 \text{ L} = 13.82 \text{ L}$
 5. Plasma volume after 1 L normal saline = $13.82 \text{ L} \times 0.25 = 3.46 \text{ L}$
 6. Albumin ([alb]) concentration after 1 L normal saline = $(3.21/3.46) \times 4.40 \text{ g/dL} = 4.08 \text{ g/dL}$
 7. Inorganic phosphate ($[P_i]$) concentration after 1 L normal saline = $(3.21/3.46) \times 1.16 \text{ mmol/L} = 1.08 \text{ mmol/L}$
 8. Total citrate ([citrate]) concentration after 1 L normal saline = $(3.21/3.46) \times 0.135 \text{ mmol/L} = 0.125 \text{ mmol/L}$
- C. Figge-Fencel quantitative physicochemical model after 1 L normal saline:
1. pH (standard state) = $f_{pH}(PCO_2, SID_{ss}, [alb], [P_i], [citrate]) = f_{pH}(40 \text{ mm Hg}, 38.9 \text{ mEq/L}, 4.40 \text{ g/dL}, 1.16 \text{ mmol/L}, 0.135 \text{ mmol/L}) = 7.40$
 2. pH' (after 1 L normal saline) = $f_{pH}(PCO_2, SID_{ad}, [alb]', [P_i]', [citrate]') = f_{pH}(40 \text{ mm Hg}, 36.09, 4.08, 1.08, 0.125) = 7.37$
- D. Actual bicarbonate (mEq/L) = $\text{Log} [HCO_3^- (\text{mEq/L})] =$
 $pH + \text{Log} (PCO_2 [\text{mm Hg}] \times 0.0307) - 6.1$
1. $[HCO_3^-]'$ (after 1 L normal saline) = 22.9 mEq/L
- E. SBE (mEq/L) = $0.9287 \times ([HCO_3^- (\text{mEq/L})]' - 24.4 +$
 $14.83 \times [pH' - 7.4])$
1. SBE (1 L normal saline) = -1.8 mEq/L

Dr Vladimir Fencel MD; a physician-teacher whose presence in the field of acid-base is missed.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

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Acknowledgement

We gratefully acknowledge the kind assistance of James Figge MD, for insightful discussions in the preparation of this manuscript and

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