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A critique of Stewart's approach: the chemical mechanism of dilutional acidosis

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Abstract *Objective:* While Stewart's acid-base approach is increasingly used in clinical practice, it has also led to new controversies. Acid-base disorders can be seen from different viewpoints: on the diagnostic/clinical, quantitative/mathematical, or the mechanistic level. In recent years, confusion in the interpretation and terminology of Stewart's approach has arisen from mixing these different levels. This will be demonstrated on the basis of a detailed analysis of the mechanism of "dilutional acidosis." In the classical dilution concept, metabolic acidosis after resuscitation with large volumes is attributed to the dilution of serum bicarbonate. However, Stewart's approach rejects this explanation and offers an alternative one that is based on a decrease in a "strong ion difference." This mechanistic explanation is questionable for principal chemical reasons. The objective of this study is to clarify the chemical mechanism of dilutional acidosis. *Methods:* Experimental data and simulations of various dilution experiments, as well as theoretical and chemical considerations were used. *Results:* 1. The key to understanding the mechanism of dilutional acidosis lies in the open CO_2/HCO_3^--buffer system where the buffer base (HCO_3^-) is diluted whereas the buffer acid is not diluted (constant pCO_2). 2. The categorization in independent and dependent variables depends on the system regarded. 3. Neither the principle of electroneutrality, nor a change in [SID], nor increased H_2O dissociation plays a mechanistic role. *Conclusion:* Stewart's approach is valid at the mathematical level but does not provide any mechanistic insights. However, the quantification and categorization of acid-base disorders, using Stewart approach, may be helpful in clinical practice.

Keywords Volume expansion · Infusion solutions · Stewart's approach · Strong ion difference · Bicarbonate · Acid-base

Introduction

In 1978, Stewart [1] introduced a new acid-base model that was further modified by Figge and Fencl [2], Watson [3], and Constable [4], and became increasingly used in clinical practice, particularly in intensive care medicine. This new model, referred to as "Stewart's approach", "physicochemical model "or "strong ion model", should enable a better quantification and mechanistic understanding of acid-base disorders than the traditional acid-base models (bicarbonate or base access approaches). Indeed it provides a mathematical formula allowing

detailed quantifications of several metabolic acid-base disorders and presents the strong ions (mainly sodium [Na^+] and chloride [Cl^-]) as new acid-base entities.

However, objections have been raised to the proposed mechanistic explanations provided by Stewart's approach [5–8]. Because current reviews, articles, and text books highlight the alleged mechanistic insight to acid-base physiology as its main strength and advantage over the traditional model [9–15], the physicochemical validity of its mechanistic explanations must be proven. This will be done in the present study on the basis of the mechanistic analysis of dilutional acidosis. In this article, we will refer to the new acid-base approach as "Stewart's approach", although not all statements or arguments we attribute to "Stewart's approach" were presented by Stewart in his original work itself [1, 16, 17] but are partly statements of proponents who further developed his acid-base approach.

Large volumes of crystalloid infusions are commonly associated with metabolic acidosis in critical illness. However, there has been a dispute about the causal mechanisms [18–21]. Originally, the phenomenon of metabolic acidosis after crystalloid infusion was attributed to the dilution of serum bicarbonate and was therefore termed, "dilutional acidosis" [22–27]. This classical dilution concept for bicarbonate was rejected by proponents of Stewart's approach, which provides a "strong ion" based explanation for the mechanism of dilutional acidosis [14, 21].

Stewart's approach identified three independent variables (pCO_2, SID, and weak acids), which are assumed to be the only ones to affect acid-base balance and the dependent variables and thus pH (for details see the electronic supplement). In the context of dilutional acidosis, Stewart's approach argued that the proposed [HCO_3^-] dilution cannot cause the observed metabolic acidosis because [HCO_3^-] is a dependent variable [28, 29]. Moreover, it was argued, that blood acids and bases are diluted equally, hence dilution does not preferentially affect bicarbonate [21].

Therefore, from Stewart's perspective an alternative explanation for dilutional acidosis needed to be developed. His mechanistic explanation is based on the strong ions and the maintenance of electroneutrality. It was believed that positive or negative charges (i.e., changes of the concentrations of strong ions) influence the dissociation of H_2O [9, 28, 30, 31]. In the context of dilutional acidosis, this means dilution of plasma (which has a positive [SID] of ca. 39 mmol/L) by water or another solution with a [SID] of zero decreases the [SID], i.e., diminishes the surplus of positive charges. However, the decrease in [SID] demands compensation by a positive charge. This is suggested by increased H_2O dissociation with generation of a positively charged H^+. This newly generated H^+ then causes acidification of the solution, i.e., dilutional acidosis [28, 30–32].

This thesis would add new insights into the mechanism of dilutional acidosis. The focus on SID offers a novel explanation for dilutional acidosis that differs from the original focus on dilution of bicarbonate and provides a simple physicochemical mechanism for what occurs when a neutral solution (e.g., saline or water, pH 6.8 at 37°C) is added to an alkaline solution (e.g., plasma, pH 7.4 at 37°C). But even more important, it represents a provoking physicochemical novelty because analyzing the consequences of this mechanism leads to an acid-base understanding and terminology, which is not concordant with standard acid-base definitions in chemistry.

The objective of this study is to clarify the chemical mechanism of dilutional acidosis. Particularly, we wanted to determine whether the SID-induced increase in H_2O dissociation causes dilutional acidosis and whether bicarbonate should be regarded as a dependent or independent variable. Finally, this analysis will be used to clarify several misconceptions arising around Stewart's acid-base approach. This study is based on simulations of dilution experiments, theoretical considerations, and in vitro experiments.

Methods

Some methodological aspects and definitions of this study should be mentioned ahead. First, at electrolyte concentrations of 0.3 mol/L (as in human blood), in physical chemistry it is obligatory to use activities instead of concentrations for acid-base calculations. In medicine, the concept of activity is traditionally ignored and concentrations are used. This might be justifiable because changes in blood osmolality in humans are small (range of osmolality 0.25–0.35 mol/L) and the resulting errors may be constant. For all acid-base calculations in this work, concentrations are used. Second, the blood plasma is considered as an isolated system/compartment, which is "diluted". Secondary processes or regulatory mechanisms induced by dilutional acidosis such as intracellular buffering and renal or respiratory compensatory mechanisms are not considered because they are not relevant for this mechanistic problem.

A pH neutral solution is defined as a solution containing equal amounts of [H^+] and [OH^-] resulting in a pH of 7.00 at standard conditions ($T = 25$°C). At standard body temperature (37°C) a neutral solution has a pH of 6.80, because water dissociation is temperature-dependent. Healthy human plasma at 37°C has a pH around 7.4, i.e., it is a slightly alkaline solution. Pure water or crystalloids with a SID of zero (e.g., normal saline) have a pH of 7.0 at 25°C and 6.80 at 37°C and are, therefore, neutral. Hence, in the case of plasma dilution by saline, an alkaline solution is mixed with a neutral solution. Acid-base relevant

Table 1 Acid-base relevant key statements of Stewart's approach and standard physical chemistry

Definitions/key statements	Stewart's approach	Standard physical chemistry [34, 44]
Acids and bases	Anions are acids, Cations are bases	Acids are proton donors, Bases are proton acceptors
Neutrality	$[OH^-] = [H^+]$, pH = 6.8 (37°C)	$[OH^-] = [H^+]$, pH = 6.8 (37°C)
Buffer-system	Weak acid	Mixture of relevant amounts of both weak acid and its conjugate base
pH calculation	Mass and charge balancing method	Mass and charge balancing method
Important parameters	Independent parameters (SID, pCO_2, weak acids)	Acids, bases, buffers, solvent
Regulating mechanisms	Change in independent parameters	H^+ transport/excretion, change of buffer/weak acids concentrations
Driving forces	Maintenance of electroneutrality	Chemical equilibrium (Gibbs energy)
Theoretical background	Mathematical correlation	Consideration of biological, physiological and chemical mechanisms

SID strong ion difference, *pCO_2* partial pressure of carbon dioxide

Table 2 Dilutional experiments

Simulation	Solution	Diluent
1	NaOH unbuffered (A)	Water (I)
2	$NaCl/NaHCO_3$ buffered with HCO_3^-/CO_2 (B), open system	Water (I)
3	$NaCl/NaHCO_3$ buffered with HCO_3^-/CO_2 (B), open system	0.9% saline (II)
4	$NaCl/NaHCO_3$ buffered with HCO_3^-/CO_2 (B), closed system	0.9% saline (II)
5	$NaCl/NaHCO_3$ + HA buffered with HCO_3^-/CO_2 (C), open system	0.9% saline (II)

NaCl sodium chloride, *$NaHCO_3$* sodium hydrogen carbonate, *HCO_3^-* bicarbonate, *CO_2* carbon dioxide, *HA* weak acid

definitions of Stewart's approach and standard physical chemistry are compared in Table 1.

To demonstrate and study the chemical processes involved in dilution, five different dilutional experiments with increasing complexity (see Table 2) are used.

Simulation 1. Solution A is 1 L of a 0.14 molar sodium hydroxide solution in the absence of CO_2. It is diluted by 1 L of pure water. This simple solution enables us to observe the chemical processes without the effects of the CO_2/HCO_3^- buffer system.

Simulation 2. Solution B is a HCO_3^-/CO_2 buffered solution with a surplus of strong base (NaOH). This solution can be generated in two different ways: (1) mixing 0.5 L of 280 mmol/L sodium hydroxide solution and 0.5 L of 210 mmol/L hydrochloric acid results in an alkaline solution containing 140 mmol/L of sodium $[Na^+]$ and 105 mmol/L chloride $[Cl^-]$. In the presence of an atmosphere containing CO_2 at a constant partial pressure (pCO_2) of 40 mmHg, the dissolved CO_2 (carbonic acid) will react with the hydroxide ions to form the bicarbonate buffered solution B containing 0.35 mmol/L $[HCO_3^-]$. (2) Dissolving 105 mmol of NaCl and 35 mmol of $NaHCO_3$ in 1 L of pure water in the presence of an atmosphere containing 40 mmHg CO_2 gives solution B. Accounting for the open CO_2 equilibrated system, the diluent initially has to be equilibrated to CO_2 (pCO_2 = 40 mmHg). The dilutional reaction occurs in the second step. The constant pCO_2 simulates an open buffer system, which is analogous to humans.

Simulation 3. Similar to simulation 2, solution B is now diluted by a 0.9% saline solution.

Simulation 4. Similar to simulation 3, 1 L of solution B is diluted by 1 L of 0.9% saline solution, but a closed system buffer system is assumed, i.e., there is no equilibration of the diluent and the resulting solution to a pCO_2 of 40 mmHg. The total amount of the CO_2-system is determined by the initial amount contained in solution B.

Simulation 5. Solution C, which is very similar to plasma (i.e., solution B plus a weak acid), is diluted by 1 L of 0.9% saline solution under open buffer conditions (pCO_2 = 40 mmHg). According to Watson [3], albumin is regarded as a protein with 16 acid-base relevant histidine residues with an approximated mean dissociation constant K_A. In this simulation, the easy available weak acid cholic acid (pK_A 6.75 at 37°C) was used instead of albumin, so that a comparable experimental setting could be established.

To elucidate the chemical reactions involved in these 'dilutional processes', we calculated the concentrations and molar amounts of the involved components before and after dilution. Total CO_2 is calculated as the sum of $[CO_3^{2-}]$. $[HCO_3^-]$, $[H_2CO_3]$ and dissolved CO_2. $[H_2CO_3]$ and dissolved CO_2 are calculated from the pCO_2 with the equilibrium constants $K_{H_2CO_3}$ and K_{diss} [33]. We also described the fictitious moment when solution and diluent have been mixed, but no chemical reaction occurred. This

fictitious moment is necessary to make quantitative considerations and understand what happens during the dilutional process.

All solutions were constructed and pH calculations were performed with standard methods of chemistry [34] using chemical equilibria equations, mass and charge balances (see appendix of the electronic supplementary material, ESM). The cubic/quartic equations were solved by computer software (Mathematica version 5.2, Wolfram Research, Champaign, USA). Additionally, all simulations where calculated by Watson's acid-base software [33].

In vitro experiments were performed for simulations 2 through 5. For preparation of the acid-base solutions the following reagents were used: bidistilled water (Aqua bidest, Fresenius Kabi Austria GmbH, Austria), 0.9% saline (Physiologische Kochsalzloesung, Fresenius Kabi Austria GmbH, Austria), 1 molar sodium hydroxide solution (No. 31,951-1, Aldrich, Germany), and cholic acid (No. 27010, BioChemica, Switzerland). One L of solution B was prepared by mixing 682 mL 0.9% saline, 35 mL 1 M $NaHCO_3$, and 283 mL water. One L of solution C was prepared by mixing 682 mL 0.9% saline, 35 mL 1 M $NaHCO_3$, 3.95 g cholic acid, and 283 mL water. Solutions were equilibrated with CO_2 in a cell incubator (37°C, relative humidity >95%, CO_2 level 5.3%). The dilutional experiment for simulation 4 (closed system) was performed by diluting solution B with diluent II (stored under CO_2 free air) in a closed syringe. Samples were measured with a blood gas analyzer (ABL 725, Radiometer®, Copenhagen, Denmark). For every simulation four samples were available (preparation of solutions and dilutional experiments were performed twice, respectively). Experimental data are presented as mean values ± standard deviation. No quantitative accounting for the individual electrolytes (as done for simulations) was done because inherent experimental and measurement inaccuracies do not allow precise enough quantitative assessment.

Results

Simulation 1 shows the dilution of the strong base, sodium hydroxide (solution A), by water (diluent I). The concentrations and molar amounts of the acid base relevant components are shown in Table S1 (see ESM). In a solution of a strong base in absence of a buffer, the concentration of OH^- will equal the total concentration of a strong base (fully dissociated) and the concentration of H^+ is negligible. Mixing solution A with diluent I and before the two solutions react, the molar amount of H^+ is drastically increased due to the large molar amount of H^+ in the added water (about 10^6 times higher than in solution A). However, after the chemical equilibrium is reached (according the ion product of water), the molar amount of H^+ is by far smaller than the molar amount of H^+ contained in the added water. Consequently, H^+ had to react with another species, which is the strongest base present and available in relevant concentrations. In this case, the only chemically logical reaction is the one with OH^-. This means increased H_2O generation from OH^- and H^+:

$$H^+ + OH^- \rightarrow H_2O \quad \text{(E2)}$$

The molar amount of OH^- is left almost unchanged because it is much larger than the molar amount of H^+. Consequently, the resulting H^+ concentration has increased due to the dilution of the strong base and the added amount of H^+. SID is decreased due to the dilution of $[Na^+]$. The observed chemical processes are in vast contrast to the theory suggested by Stewart, in which the increased dissociation of H_2O into H^+ and OH^- due to decreased SID occurs. While the solution's SID decreases, H_2O dissociation does not increase, instead new H_2O is being generated.

Simulation and experiment 2 shows the dilution of a sodium bicarbonate buffer system in a saline solution (solution B) by water (see ESM Table S2), which results in acidification. With respect to the buffer system, the buffer base concentration (HCO_3^{2-}) is halved, whereas the buffer free acid (H_2CO_3) is kept constant ($pCO_2 = 40$ mmHg). Before the chemical reaction, the molar amount of H^+ is drastically increased due to the large molar amount of H^+ contained in the added water, which results from equilibration with CO_2. After the chemical reaction, the molar amount of H^+ is significantly smaller than the molar amount of H^+ contained in the added water. The destination of H^+ is obviously the buffer contained in the solution. The concentration of OH^- is 100 times smaller than H^+ and cannot be a reasonable reactant for H^+. In the presence of the CO_2/HCO_3^- buffer system, CO_3^{2-} is the primary base (CO_3^{2-}: strongest base available in relevant concentrations) reacting with the added H^+ to form HCO_3^-. Furthermore, total CO_2 content in the solution increased, which means that new CO_2 dissolves and dissociates into HCO_3^- and H^+. Therefore, the source of the HCO_3^- increase is partly due to the reaction of CO_3^{2-} with H^+ and new dissolved CO_2. The decrease in SID is an epiphenomenon; because $[Na^+]$ exceeds $[Cl^-]$, dilution will by rules of algebra reduce the difference between $[Na^+]$ and $[Cl^-]$. Therefore, this change in SID is merely a marker of dilution.

The dilution of solution B by normal saline (diluent II) is shown in the ESM Table S3 (*simulation and experiment 3*). The resulting acidification, concentrations, and molar amounts of the acid-base components are analogous to the dilution by pure water (diluent I). Both diluents are neutral and have a SID of zero. Ignoring the effects of different osmolality (influence on activity coefficients) both solutions have the same effect on acid-base balance.

Simulation and experiment 4 (see ESM Table S4) are similar to simulation 3 but encompasses a closed CO_2/

HCO_3^--buffer system, i.e., the total CO_2 amount is constant. There is no acidifying effect of dilution. As in simulation 2 or 3, the HCO_3^- concentration is halved; in contrast, pCO_2 is not kept constant (40 mmHg) but halved as well (20 mmHg). In this case, the autoprotolysis of water plays a major role in reaching the new acid-base dissociation equilibrium. The needed OH^- is formed by dissociation of H_2O into OH^- and H^+. The formed and some additional H^+ reacts with CO_3^{2-} and HCO_3^- resulting in a slight increase in free H_2CO_3 and dissolved CO_2. This leads to a minimal increase of the partial pressure of CO_2. Actually, the resulting pCO_2 is not exactly 20 mmHg but 20.01 mmHg.

Simulation and experiment 5 mimics a solution that is similar to plasma (see ESM Table S5). Instead of the weak acid albumin cholic acid was used ($K_A = 5.62 \times 10^{-07}$ mol/L at 37°C). Similar to simulation 3, the surplus of H^+ added by diluent II reacts with the buffer base CO_3^{2-} to form HCO_3^-. However, the resulting acidification has an effect on the dissociation equilibrium of the weak acid, HA (cholic acid). In a more acidic solution, the dissociation equilibrium is shifted to the undissociated free acid. The acid anion A^- reacts with the stronger acid, H_2CO_3/CO_2, to form the free acid HA leaving one molecule HCO_3^-. This H^+ consuming mechanism leads to the small alleviation of acidification. Therefore, the increase in HCO_3^- is due to reactions of the weak acid during dilution. Similar to all other simulations, the change in SID is an algebraic necessity and hence merely a marker of dilution.

All calculations yielded similar results using Watson's acid-base model [3].

Discussion

The major objective of this study is to clarify the chemical mechanism of dilutional acidosis and, in particular, to analyze the mechanistic explanations provided by Stewart's acid-base approach. We found that the key to understanding dilutional acidosis lies in the open CO_2/HCO_3^--buffer system (simulation 2 and 4) where the buffer base ($[HCO_3^-]$) is diluted whereas the buffer acid is not diluted (constant pCO_2). The categorization in dependent and independent variables depend on the system and bicarbonate can be regarded as an independent parameter. Stewart's strong ion approach does not provide mechanistic insights to dilutional acidosis.

The mathematical level of Stewart's approach

The major new contribution of Stewart to acid-base balance was the introduction of his master equation linking several acid-base relevant components of blood plasma. This equation is based on standard methods of physical chemistry for pH calculations, i.e., combining equations for chemical equilibria and mass and charge balance (see electronic supplement). Currently, three different modifications varying in their treatment of weak acids exist: the Figge model [2, 35], Constable's simplified strong ion model [4], and Watson's single-association constant model [3]. It has been shown that these equations are correct and that the Stewart's approach and the traditional approaches are quantitatively identical [8, 36, 37]. In this study, the Watson model was used which is, in our opinion, the most practical one.

The mechanistic levels of dilutional acidosis

Examining the mechanism of dilutional acidosis, we have to define the system that is regarded. When examining the acid-base status of human blood plasma from a chemical point of view, we are confronted with ionic equilibrium reactions in an aqueous solution involving strong and weak acids. Therefore, the blood plasma is regarded as a "physicochemical" solution in an isolated compartment that is diluted. If we proceed to the more physiological setting, the expected acidosis based on plasma (bicarbonate) dilution is ameliorated by "buffering" effects of erythrocytes and interstitial fluids, which has been shown by Lang and Zander for acute normovolemic hemodilution [38]. Based on a revised classical dilution concept for bicarbonate, they could calculate and predict expected in vivo bicarbonate plasma levels for dilutional acidosis with good correlation to patient data. If we now regard living humans, we also have to consider organ function as secondary processes such as renal or respiratory compensatory mechanisms. Can we really expect Stewart's approach, which is based on a mathematical model of a physicochemical system, to clarify the mechanisms of dilutional acidosis in vivo?

Coming back to Stewart's approach and the physicochemical level of dilutional acidosis, we have to identify all blood plasma components participating in acid-base equilibrium and linking them by chemical equations and equilibrium constants. The relevant acid-base components in human plasma, dissociation equilibria, and equilibrium constants are well known and characterized, which enables theoretical simulations of the dilutional processes. In vivo or in vitro dilutional experiments are not absolutely necessary to clarify the underlying chemical mechanism. Nevertheless, data from in vitro experiments for some simulations are provided to support the theoretical data.

In all simulations, alkaline solutions were diluted by a neutral (more acidic) solution. Except in simulation 1, all solutions were buffered. Simulations 2, 3, and 5 contained an open CO_2/HCO_3^- buffer system whereas a closed CO_2/HCO_3^- buffer system was used in simulation 4.

The dilution of an unbuffered alkaline solution (simulation 1) by a neutral diluent resulted in acidification (less alkalinity), whereas dilution of a buffered system with constant amounts of buffer components (CO_2 and HCO_3^-), as in simulation 4 (closed buffer system), does not change pH. If dilution of a CO_2/HCO_3^- buffered solution occurs in open buffer conditions (simulation 2 and 3), i.e., constant pCO_2, one buffer component is diluted ($[HCO_3^-]$ halved) whereas the other buffer component is kept constant (constant pCO_2), which results in acidosis. This imbalance in the dilution of the buffer components results in a change in pH. If the buffer base is diluted and the buffer acid is kept constant, this imbalance results in acidification, which is the case in the physiologic CO_2/HCO_3^- buffer system or in the SO_2/HSO_3^- buffer system (see Table 3). Whereas in buffer systems where the buffer base is the gaseous component and is kept constant, e.g., a NH_4^+/NH_3 buffer system, dilution (by a neutral diluent) of such a solution results in alkalinisation (see Table 3, calculations are presented in the appendix of the ESM).

In simulation 5, a weak acid is present (cholic acid). This weak acid cannot be regarded as a component of a relevant buffer system since not both the free weak acid (HA) and the corresponding anion (A^-, buffer base), are present in high concentrations. Therefore, the concentration of these two components are interdependent and, furthermore, dependent on changes of pH. Therefore, the acidification during dilution in simulation 5 results in a change of the concentrations of HA and A^-. HA is formed by the reaction of A^- with the stronger acid H_2CO_3 leaving one molecule of HCO_3^- behind. This is also the reason why a change of pCO_2 in plasma, which contains the weak acid albumin (here cholic acid), leads to a change of HCO_3^-. HCO_3^- does not directly respond to changes of pCO_2 in the physiological range but a higher concentration of CO_2/acidification of plasma leads to a reaction of CO_2 (H_2CO_3) with weak acid anions resulting in a formation in HCO_3^-. This indirect interdependence of pCO_2 and HCO_3^- was already described in a criticism of Stewart's approach by Siggaard-Andersen [5].

We showed that the chemical processes after dilution of plasma by saline are identical to those after dilution by water. This also applies to other crystalloids unless they do not have a neutral pH or contain a buffer (e.g., HCO_3^- containing solutions). Morgan and colleagues showed that the acid-base effect of a crystalloid is determined by its SID in vitro [39]. This is not surprising because the [SID] was exclusively constituted by $[HCO_3^-]$ in Morgan's study. Different levels of $[HCO_3^-]$ in the diluent led to different concentrations of $[HCO_3^-]$ in the diluted solution. It has been stated that a diluent that should be neutral with respect to its dilutional effects (pH neutral), should have a [SID] of about 24 mmol/L [39]. This is exactly the physiological HCO_3^- concentration. Consequently, dilution by such a solution would neither change pCO_2 nor the HCO_3^- concentration and, therefore, has no acidifying effect. This was already noted by Zander [40].

Furthermore, in all experiments, it could be clearly shown that the change in [SID] is only an algebraic necessity or marker of dilution but has not an active or causative role in the mechanism of dilutional acidosis.

Table 3 Dilutional effects in a solution buffered with an open buffer-system comprising a gaseous and an ionic component by saline solution

Temperature 25°C	Solution (1 L)	Diluent (1 L of 0.9% saline solution)	Diluted solution
Solution with a $SO_2/NaHSO_3$ buffer system			
pH	2.490	1.954	2.268
pSO_2 (mmHg)	4	4	4
$[Na^+]$ (mol/L)	3.50E−02	1.54E−01	9.45E−02
$[HSO_3^-]$ (mol/L)	3.82E−02	1.11E−02	2.29E−02
Solution with a NH_4/NH_3 buffer system			
pH	10.199	11.373	10.494
pNH_3 (mmHg)	4	4	4
$[Cl^-]$ (mol/L)	3.50E−02	1.54E−01	9.45E−02
$[NH_4^+]$ (mol/L)	3.52E−02	2.36E−03	1.78E−02

The gaseous component is kept constant by a constant partial pressure, the other buffer component is diluted. If the gaseous buffer component is the acid (SO_2) dilution results in an acidification. If the gaseous buffer component is the base (NH_3) dilution results in an alkalinization

pNH_3 partial pressure of ammonia, NH_4^+ ammonium ion, pSO_2 partial pressure of sulphur dioxide, HSO_3^- hydrogen sulfit ion. Equilibrium constants: $K_{c(SO_2)}$: combined equilibrium and solubility constant of SO_2, $K_{2(H_2SO_3)}$: second dissociation constant of sulfurous acid, $K_{c(NH_3)}$: combined equilibrium and solubility constant of NH_3

The diagnostic and clinical level of acid-base disorders

At the beginning of a diagnostic approach to an acid-base disorder, we take a blood sample to measure H^+ concentration and pCO_2 and, depending on the model, further parameters such as haemoglobin fractions, electrolytes, albumin, lactate, etc. From these parameters several parameters used for acid-base interpretation can be calculated ($[HCO_3^-]$, standard base excess, [SID], anion gap, etc.). Of note, this measurement is a snapshot of an isolated plasma or serum (i.e., a physicochemical solution) from which we try to get clues about the underlying pathophysiology of a patient's disease process in the whole body. It is not possible to measure HCO_3^- ions exchanged by red blood cell buffering or protons originating form lactic acid production, but we can only determine the final overall result of several processes. Therefore, the primary approach to an acid-base disorder should be descriptive and not mechanistic.

All acid-base approaches describe a respiratory part (change in pCO_2) and a metabolic part (change in standard bicarbonate ($\Delta stHCO_3^-$), change in buffer base (BE) or change in strong ion difference (Δ[SID]) of acid-base disorders). For constant noncarbonated buffers it has been shown that $\Delta stHCO_3^-$, BE and ΔSID are equal [37]. For additional information on changes of other ions the anion gap (AG) or the albumin corrected anion gap (AG_{corr}) are used in the classical models. The advantage of Stewart's approach is that all the additional information can be extracted from the single master equation and that it provides the most comprehensive description of changes in noncarbonated buffers (albumin and phosphate). With Stewart's master equation, it is possible to calculate base excess subsets allowing a comparable quantification of several metabolic components and even the respiratory part of acid-base derangements [41].

Therefore, in our opinion, a description of acid-base disorders on the basis of Stewart's categorization is very useful [10, 42]. However, one has to keep in mind that this categorization is only descriptive and not mechanistic. For example, in dilutional acidosis a decreased [SID] (or hyponatremic acidosis) can be found [43]; however, this does not mean that low serum sodium concentration is the cause of the acidosis. Analogously, a hyperchloremic acidosis can have several causes, but is not caused by chloride; chloride is not acidic. The causes and compensational mechanisms of acid-base disorders can only be explained by the clinical situation and pathophysiological considerations, but not by a mathematic formula.

Summary and conclusions

The chemical mechanism of dilutional acidosis when focusing on blood plasma is the dilution of an open CO_2/HCO_3^- buffer system where the buffer base (HCO_3^-) is diluted but not the buffer acid (CO_2). This 'unbalanced' buffer dilution results in acidosis. A change in [SID], which is a mathematical construct, does not cause dilutional acidosis but is merely a marker for the dilutional process. Furthermore, we demonstrated that increased water dissociation is not the chemical mechanism of dilutional acidosis and Stewart's approach does not provide any mechanistic insights into acid-base disorders. The distinction of "independent variables" and "dependent variables" by Stewart is arbitrary and depends on the regarded system (see ESM). Some say that Stewart's approach, the strong ion approach, is just a different (and easier to understand) view on the same processes leading, in the end, to the same quantitative results. This is partly true, because the formulae used in Stewart's approach are based on classical physical chemistry and are concordant with the traditional acid-base approaches. However, Stewart's approach is disqualified by the incorrect causal and mechanistic explanations derived from these calculations. They may appear to be attractive explanations because of their simple mechanistic/mathematical principles, but one must not trade accuracy for simplicity. Consequently following these principles very quickly leads to an acid-base understanding and terminology that is not concordant with current models in chemistry and that might also be beyond the interpretations Stewart originally would have appreciated. It is important that quantitative/mathematical correlations must not be directly transformed to real mechanistic processes. Therefore, in our opinion, the Stewart's approach leads us to a more differentiated view on the metabolic part of acid-base disorders and allows detailed quantifications that may be helpful in clinical practice, but its mechanistic interpretations must be rejected.

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