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Prediction of dilutional acidosis based on the revised classical dilution concept for bicarbonate

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Lang, Werner, and Rolf Zander. Prediction of dilutional acidosis based on the revised classical dilution concept for bicarbonate. *J Appl Physiol* 98: 62–71, 2005; doi:10.1152/japplphysiol.00292.2004.—Due to the controversy surrounding the term dilutional acidosis, the classical dilution concept for bicarbonate has been rigorously revised for the prediction of pH, actual bicarbonate concentration, and base excess. In the algorithms derived for buffer solutions, blood, and whole body (1-, 2-, and 3-fluid compartment), only bicarbonate is considered. On dilution at constant P_{CO_2}, the final concentration of bicarbonate is the sum in terms of pH, due to the following processes: dilution, formation from chemical reaction with the nonbicarbonate buffers phosphate, hemoglobin, and plasma proteins, and transfer from erythrocytes and interstitial fluid to plasma. At constant P_{CO_2}, the level of carbonic acid is held constant, whereas those of the buffer bases are reduced by dilution, resulting in acidosis. In mixed bicarbonate/phosphate buffer, the final concentration of HCO_3^- exceeds the diluted value due to additional buffering of H_2CO_3 by HPO_4^{2-}. For whole blood in vitro, pH, and actual bicarbonate concentration are predicted from dilution with 0.9% saline from initial Hb (100%) to infinite dilution (pure saline). The acidosis from dilution of plasma bicarbonate is mitigated by contributions from plasma proteins (<1 mmol/l) and from the erythrocytes (~5 mmol/l). Similarly, for whole body, the main contributions to combat primary dilutional acidosis in the range of hemodilution (relative Hb: 100–50%) are from the erythrocytes (1.2–2.2 mmol/l) and from the interstitial fluid (3.3–7.2 mmol/l). Perioperatively measured nonrespiratory acidosis is predictable if caused by hemodilution with fluids containing neither bicarbonate nor its precursors, irrespective of other electrolytes.

volume expansion; volume replacement; acute normovolemic hemodilution; infusion solutions

EFFECTS FROM LARGE AMOUNTS of crystalloid or colloid infusions into patients are manifold: decreased total protein ([Pr]) and hemoglobin ([Hb]) levels in blood and plasma, and changes in acid-base and electrolyte status. Many of the acid-base variables, pH, P_{CO_2}, and P_{O_2}, as well as many of the electrolytes, sodium, potassium, ionized calcium, chloride, and lactate, can be easily obtained by use of modern analyzing technique. Traditionally, the decrease in pH and the negative base excess (BE), e.g., from infusion of 0.9% saline, is called dilutional acidosis. In the clinical setting, however, it had generally been ignored, due to the widespread opinion that the decrease in plasma bicarbonate concentration ($[HCO_3^-]$) is only small (2–3 mmol/l), compared with the large extracellular fluid (ECF) expansion (30%) (15, 17). It was not until the nineties when the subject was rediscovered and soon became a matter of controversial discussions, both in view of the modern Stewart approach of acid-base and, conventionally, according to Henderson-Hasselbalch (HH) and Siggaard-Andersen (5, 9, 10).

The new contribution of the Stewart approach (3, 19) is the distinction between independent variables, P_{CO_2}, the strong ion difference (SID), and the total concentration of nonvolatile acid ($[A]_{tot}$) in the plasma, and dependent variables, pH, $[HCO_3^-]$, and others. The latter are completely determined by the independent variables and can only change if these are altered. For example, nonrespiratory acidosis from dilution with 0.9% saline is explained by a decrease in $[A]_{tot}$, causing metabolic alkalosis, and a decrease in the SID, causing metabolic acidosis, which is prevailing (2). In this case, dilutional acidosis is characterized by high-chloride concentration (hyperchloremia) and low $[HCO_3^-]$ (hypobicarbonatemia) in the plasma, called hyperchloremic metabolic acidosis. It is also clear that, for prediction of plasma pH or actual $[HCO_3^-]$ after hemodilution at constant P_{CO_2}, prior predictions of the independent variables, $[A]_{tot}$ and SID, are necessary. For the SID, however, this comprises several ions (e.g., sodium, potassium, calcium, chloride, lactate) of which the concentrations may be decreased or increased by dilution, depending on the composition of the diluent and urinary excretion, and from movements between different compartments (plasma and erythrocytes; plasma and interstitial and intracellular fluid). Because those predictions are complex without extended measurements, HCO_3^- is preferred as a key ion, even though it is a dependent variable.

In the conventional approach of dilutional acidosis (1, 15, 16), $[HCO_3^-]$ in the plasma is the basic quantity, which is decreased from dilution at constant P_{CO_2}. Thus, in the HH equation, the normal acid-base ratio is changed, and pH decreases. However, quantitative prediction of the pH from simple dilution fails, and the effects from saline administration in vivo, as well as from in vitro dilution of blood, plasma, and buffer solutions, were described only empirically (4). In clinical practice, the pH, BE, and also many other variables measured in the course of hemodilution are unspecific and may include additional effects from acid-base disorders (renal, intestinal, or metabolic). This makes diagnosis often difficult and prevents critical examination of the benefits in outcome of the used resuscitation fluids.

Therefore, the classical dilution concept for HCO_3^- was reexamined and rigorously revised to allow quantitative predictions of pH, actual $[HCO_3^-]$, and also BE from dilution with HCO_3^--free fluids at constant P_{CO_2}. In the revised dilution concept, HCO_3^- is the central and the only ion that is consequently treated as a subject of dilution, HCO_3^- formation from buffering, and redistribution by transfer between the different fluid compartments. This was demonstrated by theoretical calculations for the following systems with increasing degree of complexity (1-, 2-, and 3-fluid compartment): *1*) buffer solutions, containing HCO_3^-/carbonic acid; *2*) blood in vitro; and *3*) whole body. For whole

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blood and whole body, the fluid compartments are red cell volume (RCV), plasma volume (PV), and interstitial fluid (ISF) volume (ISV), respectively. The large intracellular volume, other than erythrocytes, is not included and is treated only as a source of carbon dioxide for equilibration of the surrounding fluids. Both the formation of HCO_3^- from chemical reaction at constant P_{CO_2} in buffer solution (phosphate), plasma (protein), and erythrocytes (Hb), as well as the distribution of HCO_3^- between erythrocytes and plasma (r_C), are derived in terms of pH from known empirical equations (17, 20), whereas the Gibbs-Donnan factor (D–) for the distribution of HCO_3^- between ISF and plasma is assumed to be constant. For prediction of dilutional acidosis in whole body, the following input variables are needed: measured values (pH, P_{CO_2}, [Pr], and [Hb] before and after hemodilution) and estimated values (from body weight: blood, plasma, interstitial and extracellular volume), as well as infused and exchanged volume, blood loss, and urinary volume. Concentrations of plasma electrolytes other than HCO_3^- are not necessary, even though they were useful in calculating the independent variables in the Stewart approach for comparison. It was argued that, if nonrespiratory acidosis is in agreement between predicted and reported, it must be of dilutional origin. This was tested by comparison with available literature data for whole blood in vitro and from appropriate recent clinical studies chosen according to the following criteria: *1*) pure volume expansion (hypervolemia), i.e., only infusion, no blood loss, no surgery [Waters and Bernstein (21)]; *2*) combined volume expansion + blood loss, i.e., surgery [Scheingraber et al. (14)]; and *3*) acute normovolemic hemodilution (ANH), i.e., blood exchange, blood loss, surgery [Singbartl et al. (18) and Rehm et al. (12)].

Glossary

ANH	Acute normovolemic hemodilution
$[A]_{tot}$	Total plasma concentration of nonvolatile acid (mmol/l)
BE	Whole blood base excess (mmol/l)
BV, BV_o	Final and initial blood volume (liters), respectively
BV_{out}	Lost blood volume (liters)
ΔC_E	Change in bicarbonate concentration in erythrocytes (mmol/l)
ΔC_{ISF}	Change in bicarbonate concentration in interstitial fluid (mmol/l)
D_-	Concentrational Gibbs-Donnan factor for bicarbonate (plasma/interstitial fluid)
ECV, ECV_o	Final and initial extracellular volume (liters), respectively
F_{ISF}	Dilution factor for interstitial fluid
F_P	Dilution factor for plasma
[Hb], $[Hb]_o$	Final and initial total Hb concentration in blood (g/dl), respectively
$[HCO_3^-(P)]$, $[HCO_3^-(E)]$, $[HCO_3^-(ISF)]$	Final concentration of bicarbonate (mmol/l) in plasma (P), erythrocytes (E), or interstitial fluid (ISF), respectively
$[HCO_3^-(P)]_o$, $[HCO_3^-(E)]_o$, $[HCO_3^-(ISF)]_o$	Initial concentration of bicarbonate (mmol/l) in plasma (P), erythrocytes (E), or interstitial fluid (ISF), respectively
Hct, Hct_o	Final and initial hematocrit (dimensionless or %), respectively
Hct_{out}	Hematocrit in lost blood
ISV, ISV_o	Final and initial interstitial fluid volume (liters), respectively
MCHC	Mean cellular Hb concentration (g/l or mmol/l)
pK, pK_1	Negative logarithm to base 10 of apparent dissociation constant of phosphate and bicarbonate buffer
$[Pr^-(P)]$	Equivalent charges of total plasma protein (meq/l)
[Pr(P)], $[Pr(P)]_o$	Final and initial concentration of total plasma protein (g/l), respectively
PV, PV_o	Final and initial plasma volume (liters), respectively
PV_{out}	Lost plasma volume (liters)
r_C	Concentrational distribution ratio of bicarbonate ion (plasma/erythrocytes)
RCV, RCV_o	Final and initial red cell volume (liters), respectively
RCV_{out}	Lost red cell volume (liters)
sCO_2	Solubility for carbon dioxide (mmol·l^{-1}·Torr^{-1})
SID	Strong ion difference (meq/l)
UV	Urine volume (liters)
V_{in}, V_x	Infused or added volume (liters), respectively
x(E)	Concentration of formed bicarbonate in erythrocytes (mmol/l)
x(P)	Concentration of formed bicarbonate in plasma (mmol/l)

MATERIALS AND METHODS

The study was approved by the Institut für Physiologie und Pathophysiologie der Universität Mainz.

For theoretical calculations of the pH and the $[HCO_3^-]$ in the revised dilution concept, the following systems were considered.

The first system is hypothetical buffer solutions at the same total ionic strength (154 mmol/l): pure phosphate buffer (30 mmol/l)/NaCl (76 mmol/l), consisting of buffer base (Na_2HPO_4: 24 mmol/l), and buffer acid (NaH_2PO_4: 6 mmol/l); pure sodium bicarbonate (24 mmol/l)/NaCl (130 mmol/l); and combined buffer of sodium bicarbonate (24 mmol/l) and phosphate (30 mmol/l)/NaCl (52 mmol/l).

The second system is whole blood in vitro: normal blood with total [Hb] (15.2 g/dl), hematocrit (0.455), and zero BE. The [Pr] was assumed to be 70 g/l. Data for comparison were taken from Zander (23).

The third system is whole body. Data were taken from published recent clinical studies (12, 14, 18, 21).

In the revised dilution concept, the central quantity is the $[HCO_3^-]$ in the solution and in the plasma for whole blood in vitro and for whole body. On dilution at constant P_{CO_2}, it is first decreased in accordance with the dilution factor (F_{dil}), followed by chemical interaction of the carbonic acid with available nonvolatile buffers in the solution or in the plasma and erythrocytes to form HCO_3^- and redistribution by transfer of HCO_3^- between erythrocytes and plasma and between ISF and plasma. This can be expressed in an equation. After dilution at final plasma pH, the final $[HCO_3^-]$ in the plasma is the sum of the following terms:

$$[HCO_3^-] = [HCO_3^-]_{diluted} + [HCO_3^-]_{formed} + [HCO_3^-]_{transferred} \quad (1)$$

As shown in detail in the APPENDIX, the right side of *Eq. 1* can be presented as a function, depending only on pH and known quantities.

Thus both the pH and the $[HCO_3^-]$ at known P_{CO_2} are determined, if, as a second equation, the familiar HH equation is used:

$$pH = pK_1 + \log_{10}\{[HCO_3^-]/(sCO_2 \times P_{CO_2})\} \quad (2)$$

where pK_1 is apparent pK of the carbonic acid/HCO_3^- buffer, sCO_2 is the solubility factor for carbon dioxide ($mmol \cdot l^{-1} \cdot Torr^{-1}$) in the liquid phase, and the logarithm is to base 10. The method of calculation by use of *Eqs. 1* and *2* is demonstrated in the following sections.

Dilution of simple buffer solutions in a closed and in an open system. For pure phosphate and pure HCO_3^- buffer without gas phase in a closed system, dilution with normal saline is trivial. It is also trivial for a solution of pure sodium bicarbonate in an open system at fixed P_{CO_2}. Because there is no formation of HCO_3^- and no transfer, the other two terms are zero, and, according to *Eq. 1*, the new $[HCO_3^-]$ is:

$$[HCO_3^-] = [HCO_3^-]_{diluted} \quad (3)$$

where the concentration of diluted HCO_3^- is initial concentration ($[HCO_3^-]_o$) $\times$ F_{dil}, and pH is obtained from *Eq. 2*. In a combined buffer, however, consisting of HCO_3^- ($[HCO_3^-]_o$) and phosphate of total concentration (C_o), HCO_3^- is formed from chemical reaction (x) between the diluted buffer base of phosphate and carbonic acid: $HPO_4^{2-} + H_2CO_3 = H_2PO_4^- + HCO_3^-$, and the second term is not zero:

$$[HCO_3^-] = [HCO_3^-]_{diluted} + [HCO_3^-]_{formed} \quad (4)$$

Equation 4 can be given as a function of pH: $[HCO_3^-] = f_1(pH)$ (see *Eq. A1*), if the HH equation is applied to the phosphate buffer with apparent $pK = 6.8$,

$$pH = 6.8 + \log_{10}\{([HPO_4^{2-}]_{dil} - x)/([H_2PO_4^-]_{dil} + x)\} \quad (5)$$

and solved for $x = [HCO_3^-]_{formed}$. The second function for $[HCO_3^-] = f_2(pH)$, is obtained from *Eq. 2* with apparent $pK = 6.1$ and solubility factor = 0.03 assumed for the system:

$$[HCO_3^-] = 0.03 \times P_{CO_2} \times 10^{pH-6.1} \quad (6)$$

Thus, for calculation of pH and $[HCO_3^-]$, two equations exist, which can be solved from the condition that the difference, $f_1(pH) - f_2(pH)$, must be zero. This is evaluated by numerical analysis as described in the APPENDIX.

Dilution of whole blood in vitro. The dilution of whole blood in vitro by addition of 0.9% saline (V_x) to initial blood volume (BV_o) at constant P_{CO_2} is based on the assumption that only the initial PV (PV_o) is diluted, whereas the initial RCV (RCV_o) is not changed. Thus, in the first step of pure dilution (dil), all initial values (pH_o, $[Hb]_o$, $[Pr]_o$) are changed in the plasma {$PV = PV_o + V_x$, $pH_{dil} < pH_o$, $[HCO_3^-(P)]_{dil}$, and $[Pr(P)]_{dil}$} and in the blood ($BV = BV_o + V_x$ and [Hb]), but not in the erythrocytes {$RCV = RCV_o$, $pH_o(E)$, $[HCO_3^-(E)]_o$, and mean cellular [Hb] (MCHC) = total [Hb] in the erythrocytes}. The F_{dil} for plasma (F_P) is obtained from known [Hb] and hematocrit in the blood before and after dilution:

$$F_P = PV_o/PV = [BV_o \times (1 - Hct_o)]/[BV \times (1 - Hct)] \quad (7)$$
$$= \{[Hb] \times (1 - Hct_o)\}/\{[Hb]_o \times (1 - Hct)\}$$

In the next step, formation of HCO_3^- from chemical reaction takes place, both in the plasma [x(P), mmol/l]: $Pr^- + H_2CO_3 = HPr + HCO_3^-$, and in the erythrocytes [x(E), mmol/l]: $HbO_2^- + H_2CO_3 = HHbO_2 + HCO_3^-$.

The concentration of formed HCO_3^- in the plasma after dilution is equal to the decrease in the proteinate concentration and is calculated according to Thomas (20):

$$x(P) = -\Delta[Pr^-(P)] = -[Pr(P)]_{dil} \times 0.104 \times (pH - pH_o) \quad (8)$$

Similarly, in the erythrocytes, it is equal to the decrease in the oxyhemoglobinate concentration, calculated according to the equation:

$$x(E) = -\Delta[HbO_2^-(E)] = -(145.571 - 12.273 \times pH) \times (pH - pH_o) \quad (9)$$

The last step consists of transfer of HCO_3^- between the erythrocytes (E) and the plasma (P), until the new distribution is in accordance with the Donnan equilibrium at final plasma pH: $r_C = [HCO_3^-(E)]/[HCO_3^-(P)]$. For r_C, the distribution ratio of HCO_3^- as a function of pH, a known empirical relationship is used (17): $r_C = 2.642 - 0.28 \times pH$. The final $[HCO_3^-]$ in the erythrocytes (E) is:

$$[HCO_3^-(E)] = [HCO_3^-(E)]_o - \Delta C_E = r_C \times [HCO_3^-(P)] \quad (10)$$

where ΔC_E is the difference between $[HCO_3^-]_o$ and final $[HCO_3^-]$ in the erythrocytes if plasma pH changes from initial pH_o to final pH, and in the plasma:

$$[HCO_3^-(P)] = [HCO_3^-(P)]_{dil} + x(P) + RCV \times [x(E) + \Delta C_E]/PV \quad (11)$$

where the first term is the decreased $[HCO_3^-]$ from pure plasma dilution, the second is the increment from chemical reaction with plasma proteins, and the third is the increase from transfer of HCO_3^- produced in the erythrocytes. From combination of *Eqs. 10* and *11*, and substituting for r_C and rearranging, ΔC_E is expressed as a function of only pH and known quantities. To calculate pH, however, a second relationship for ΔC_E must be known. This is obtained from the HH equation for the HCO_3^-/carbonic acid system in the plasma:

$$pH = 6.1 + \log_{10}\{[HCO_3^-(P)]/(0.0304 \times P_{CO_2})\} \quad (12)$$

if $[HCO_3^-(P)]$ is substituted from *Eq. 11*. pH is then calculated from ΔC_E by variation of pH, until $\Delta C_E(1) - \Delta C_E(2)$ is equal to zero. The detailed equations are explicitly given in the APPENDIX.

Dilution in whole body. For whole body, the two-fluid compartment for whole blood in vitro is extended to a three-fluid compartment by including the ISV. It is assumed to contain no other buffers except HCO_3^-/carbonic acid, and the distribution ratio of HCO_3^- between plasma (P) and ISF at end plasma pH is determined by the D_-:

$$[HCO_3^-(P)] = D_- \times [HCO_3^-(ISF)] \quad (13)$$
$$= D_- \times \{F_{ISF} \times [HCO_3^-(ISF)]_o - \Delta C_{ISF}\}$$

In good approximation: $D_- = 1 - 0.5 \times [Pr^-(P)]/\{[Na^+(P)] + [K^+(P)]\}$. It is further assumed that only the ECF is diluted from volume infusion (V_x), i.e., the plasma ($F_P = PV_o/PV$) and the ISF ($F_{ISF} = ISV_o/ISV$), but not the RCV. Hence, $[HCO_3^-(ISF)] = F_{ISF} \times [HCO_3^-(ISF)]_o - \Delta C_{ISF}$, where ΔC_{ISF} is the change in ISF between diluted $[HCO_3^-]_o$ and final $[HCO_3^-]$. The mole number of HCO_3^-, transferred from the ISF to the plasma or vice versa and expressed as concentration in the plasma, must be added to *Eq. 11*:

$$[HCO_3^-(P)] = [HCO_3^-(P)]_{dil} + x(P) + RCV \times [x(E) + \Delta C_E]/PV + ISV \times \Delta C_{ISF}/PV \quad (14)$$

In the same way as for whole blood in vitro, the final concentration of HCO_3^- in *Eq. 14* at end-plasma pH must also fulfill both the Donnan distribution equilibrium between erythrocytes and plasma (*Eq. 10*) and the dissociation equilibrium for HCO_3^-/carbonic acid in the plasma according to HH (*Eq. 12*). Hence, if substituting for ΔC_{ISF} in *Eq. 14*, two equations are obtained for ΔC_E in whole body as a function of pH: $\Delta C_E(1)$ and $\Delta C_E(2)$. As above, the pH is found by variation until the condition $\Delta C_E(1) - \Delta C_E(2) = 0$ is satisfied, and all of the other variables, such as BE or actual $[HCO_3^-]$ in the plasma, in the erythrocytes, or in the ISF, can be predicted. For calculation of whole blood BE, the Van Slyke equation, according to Lang and Zander (6), is used.

ANH. ANH is a procedure widely used in clinical practice in which blood is removed from a patient preoperatively and simultaneously replaced with an appropriate volume of crystalloids or colloids by infusion to maintain the initial intravascular volume (BV_o). Compared

with classical dilution from infusion without blood loss, initially decreased [HCO_3^-] in the plasma is not caused from hypervolemia of the blood (BV) and ISF (ISV), but from exchange of defined blood volume out (BV_{out}) against infused volume in (V_{in}). Even though this exchange is a continuous process in interaction with the surrounding ISF and the erythrocytes, the final [HCO_3^-] at end-plasma pH is calculated in the same way as in whole body (*Eqs. 13* and *14*). It is assumed that the final state at the end of ANH is the same, irrespective of whether it is reached continuously or in one step, consisting of dilution of the $[HCO_3^-]_o$ in the plasma and in the ISF with additional formation and transfer of HCO_3^- from the erythrocytes and from the ISF to the plasma. Because decreased [Hb] is used as a measure for hemodilution ([Hb]), the F_P is the same (*Eq. 7*).

In all calculations, using the algorithm for dilution in whole body, BV_o was estimated from known body weight by an empirical formula (7). For men, BV_o (ml) = 41.0 × body weight (kg) + 1,530, and, for women, BV_o (ml) = 47.16 × body weight (kg) + 864. In both equations, the coefficient of variation is the same: ±8.9%.

RESULTS

Buffer solutions. In pure phosphate buffer (HPO_4^{2-}: 24 mmol/l; $H_2PO_4^-$: 6 mmol/l; total: 30 mmol/l) (Table 1) and also in pure HCO_3^- buffer (HCO_3^-: 24 mmol/l; CO_2: 1.2 mmol/l; total: 25.2 mmol/l) in a closed system without gas phase, the initial pH at 7.4 is not changed after dilution (1:2) with 0.9% saline. All concentrations of the corresponding buffer pairs and also of total buffer are proportionately (1:2) decreased, and, therefore, their acid-base ratios do not change.

However, in an open system at constant P_{CO_2} = 40 Torr, the concentration of the gaseous carbonic acid component is held permanently constant (CO_2: 1.2 mmol/l), whereas those of the nonvolatile buffer components are reduced, resulting in acidosis (Table 1). After dilution (1:2), the calculated pH in pure HCO_3^- buffer from halved [HCO_3^-] (12 mmol/l) is 7.1, according to HH (*Eq. 2*), and 7.154 in HCO_3^-/phosphate buffer (*Eq. A1* in the APPENDIX and *Eq. 6*). In the latter, calculation of pH from pure dilution leads to paradoxical values: 7.1 from dilution of HCO_3^-, and 7.4 from dilution of phosphate buffer. However, this discrepancy in pH is matched by formation of HCO_3^- (1.6 mmol/l) from chemical reaction. Thus, in the final state, the concentrations of HCO_3^- (13.6 mmol/l) and also of $H_2PO_4^-$ (4.6 mmol/l) are increased, whereas that of HPO_4^{2-} (10.4 mmol/l) is decreased with respect to their diluted values. Only the concentration of the total buffer bases (48 mmol/l) is diluted (1:2).

Table 1. *Hypothetical buffer solutions: pH and concentrations before and calculated after dilution with 0.9% saline and subsequent chemical reaction*

Buffer Solution	Before Dilution	After Dilution (1:2)	After Chemical Reaction
Pure phosphate			
Base: HPO_4^{2-}, mmol/l	24	12	
Acid: $H_2PO_4^-$, mmol/l	6	3	
pH	7.4	7.4	
At Constant P_{CO_2} = 40 Torr			
Pure bicarbonate			
Base: HCO_3^-, mmol/l	24	12	
Acid: CO_2,* mmol/l	1.2	1.2	
pH	7.4	7.1	
Mixed bicarbonate + phosphate			
Base: HCO_3^-/HPO_4^{2-}, mmol/l	24/24	12/12	13.6/10.4
Acid: $CO_2/H_2PO_4^-$, mmol/l	1.2/6	1.2/3	1.2/4.6
Total buffer bases, mmol/l	48	24	24
pH	7.4	7.1/7.4†	7.154

*Anhydride of the carbonic acid H_2CO_3. All values were calculated from the Henderson-Hasselbalch equation with apparent negative logarithm to base 10 of apparent dissociation constant at 37°C: 6.8 for phosphate, and 6.1 for bicarbonate buffer. †First and second value calculated from the buffer components of the bicarbonate and of the phosphate buffer in the mixture after dilution without chemical reaction.

Whole blood in vitro. In the calculations, the following acid-base variables from the literature were used (23): initial pH (7.4), P_{CO_2} (40 Torr), and total plasma protein concentration (70 g/l) before dilution, and total Hb (15.2 g/dl) before and after dilution (10.7, 6.6, 3.7 g/dl) with 0.9% saline at constant P_{CO_2}. From these and the hematocrit that was calculated from the ratio of whole blood (g/dl) to MCHC (33.4 g/dl), all of the other acid-base quantities are derived (Table 2). The F_P, running from 100% before to 56.4, 29.5, and 14.9% after dilution (*Eq. 7*), was used to calculate the diluted concentrations of the plasma proteins (39.5, 20.6, 10.4 g/l) and of the plasma HCO_3^- (13.69, 7.15, 3.62 mmol/l). Taking these concentrations and the hematocrit after dilution and the $[HCO_3^-]_o$ in the erythrocytes (13.83 mmol/l), and substituting for $r_C = 2.642 - 0.28 \times$ pH in the two equations for $\Delta C_E(1)$ and $\Delta C_E(2)$, given in the APPENDIX for whole blood in vitro, the pH, the actual [HCO_3^-] in the plasma (*Eq. 11*), and also the BE (Van Slyke equation) were calculated. The pH is strongly shifted to the acid side (7.283, 7.128, 6.945) with large negative values (−7.52, −15.21, −21.61 mmol/l) in BE. The corresponding decrease in plasma HCO_3^- from 24.26 mmol/l to 18.53, 12.96, and 8.51 mmol/l is less than proportionate to plasma dilution. This is caused by formation of HCO_3^- from the plasma proteins (0.48, 0.58, 0.49 mmol/l) and by transfer from the erythrocytes (4.36, 5.23, 4.40 mmol/l). In the erythrocytes, the formation of HCO_3^- from oxyhemoglobinate by chemical reaction is strongly increased (6.58, 15.80, 27.44 mmol/l) with decreasing plasma pH; however, the fraction of the erythrocytes (hematocrit) is also decreased as hemodilution proceeds. Hence, the transfer of HCO_3^- from the erythrocytes to the plasma must have an optimum. This was assessed by further calculations, assuming additional [Hb] (14, 12.7, 8.6, 7.6, 2.5, 1.5 g/dl). All calculated values (pH, plasma HCO_3^-, and BE) are in good agreement with reported values from the literature (23).

Whole body. The basic values, used in the algorithm to predict pH, actual [HCO_3^-] in the plasma, and whole blood BE, were derived from the chosen clinical studies in the literature (Table 3). In the major calculations for pH from $\Delta C_E(1)$ and $\Delta C_E(2)$ in whole body (APPENDIX) and for the plasma [HCO_3^-] (*Eqs. 13* and *14*), these are the $[HCO_3^-]_o$ in the erythrocytes and in the plasma; the total plasma proteins; the D_- before dilution; the F_P and the F_{ISF} (F_{ISF} = ISV/ISV_o); and the hematocrit, the PV, and the interstitial volume (ISV) after dilution. BV_o and initial volume of the ECF (ECV_o) were obtained by estimation, and RCV_o was obtained by calculation from venous, not body, hematocrit. The corresponding volumes after dilution were estimated differently, depending on the special circumstances of the clinical study. In the before-infusion column of Table 3, all initial values for pH and the [HCO_3^-] in the plasma were corrected for end-P_{CO_2} after dilution, and all values in the after-infusion column, except the hematocrit and the P_{CO_2}, were predicted.

In the clinical study by Waters and Bernstein (21), all participants within the same group of healthy volunteers received comparable amounts of two different colloids by infusion: 6% hydroxyethyl starch (HES) solution (Hetastarch: 1.095 liter), and, 4 wk later, 5% albumin solution (5% HA: 1.094 liter). Because there was no blood loss, the RCV_o was

Table 2. *Dilution of whole blood in vitro: acid-base values before and after dilution with 0.9% saline at constant P_{CO_2}*

Whole Blood In Vitro	Before Dilution	After Dilution: Final Values		
Total hemoglobin, g/dl	15.2	10.7±0.5†	6.6±0.5†	3.7±0.5†
F_P	1.000	0.564±0.039	0.295±0.028	0.149±0.023
Total plasma protein, g/l	70*	39.5	20.6	10.4
pH	7.400±0.01†	7.283±0.017‡	7.128±0.025‡	6.945±0.043‡
P_{CO_2}, Torr	40±1.5†			
Bicarbonate in plasma, mmol/l	24.26±1.07	18.53±0.71‡	12.96±0.74‡	8.51±0.85‡
From plasma dilution, mmol/l	24.26±1.07	13.69±1.06	7.15±0.73	3.62±0.57
From plasma proteins, mmol/l	0	0.48±0.04	0.58±0.02	0.49±0.03
Transfer from erythrocytes, mmol/l	0	4.36±0.37	5.23±0.13	4.40±0.27
Plasma proteinate, meq/l	16.89±1.03	9.05±0.63	4.40±0.42	2.03±0.32
pH(E)	7.190±0.008	7.100±0.013	6.981±0.019	6.840±0.033
r_C	0.570±0.003	0.603±0.005	0.646±0.008	0.697±0.012
Bicarbonate in erythrocytes, mmol/l	13.83±0.61	11.17±0.86	8.38±0.79	5.93±0.57
From oxygenated Hb, mmol/l	0	6.58±0.96	15.80±1.52	27.44±2.86
ΔC_E, mmol/l	0	2.66±0.56	5.45±0.60	7.89±0.68
Whole blood base excess, mmol/l	0	−7.52±0.96‡	−15.21±1.04‡	−21.61±1.25‡

Values are means ± SE. *Assumed value; †assumed variances in the input variables from which all others are calculated; ‡comparison with reference values (23) for pH (7.27; 7.12; 6.95), plasma bicarbonate (18.0; 12.7; 8.6 mmol/l), and base excess (−8.3; −15.6; −21.4 mmol/l). F_P, plasma dilution factor; pH(E), pH in erythrocytes; r_C, bicarbonate distribution ratio; ΔC_E, change in bicarbonate concentration between initial and final value in the erythrocytes. All values after dilution, including plasma pH, are calculated from only 4 variables: initial plasma pH, P_{CO_2}, total Hb, and total plasma protein concentration. Complete equations for pH are in the APPENDIX [$\Delta C_E(1)$ and $\Delta C_E(2)$] and in MATERIALS AND METHODS (*Eqs. 7–11*).

conserved in the Hetastarch group (2.089 liters) and in the HA group (2.063 liters), and the approximated BV values (RCV/Hct) after dilution were 5.303 and 5.033 liters, respectively. The volumes after dilution are estimated as follows: $ECV = ECV_o + V_{in}$, $PV = BV - RCV$, and $ISV = ECV - PV$.

The clinical study by Scheingraber et al. (14) featured two randomized groups of patients with gynecological surgery, blood loss, and infusion of crystalloids: 0.9% saline and lactated Ringer solution. In this case, the volumes after dilution were estimated in another way: $RCV = RCV_o - RCV_{out}$, where $RCV_{out} = BV_{out} \cdot Hct_{out}$ is the volume of the lost erythrocytes in the 2 h of surgery and infusion, and Hct_{out} is the mean hematocrit before (Hct_o) and after dilution (Hct); $BV = RCV/Hct$; $PV = BV - RCV$; $ECV = ECV_o + V_{in} - PV_{out} - UV$, where $PV_{out} = BV_{out} \cdot (1 - Hct_{out})$ is the lost PV, and UV is urine volume. In both the saline and the Ringer group, all estimated volumes of the blood, plasma, and ISF are expanded and hypervolemic.

Table 3. *Baseline data and calculated intermediate values used in the algorithm for dilution in whole body*

	Infusion					
	Before	After	Before	After	Before	After
Clinical study	Waters and Bernstein (21)		Scheingraber et al. (14)		Rehm et al. (12)	
Infused solution	Hetastarch		0.9% saline		6% HES	
No. of patients	11		13		10	
Body weight, kg	74±9		68±13		62±13	
BV, liters	4.552	5.303	4.071	4.306	3.788	3.788
Hct, %	45.9	39.4	35.9	26.9	34.1	21.9
RCV, liters	2.089	2.089	1.463	1.160	1.292	0.829
PV, liters	2.463	3.213	2.608	3.145	2.496	2.959
ECV, liters	14.740	15.835	13.600	17.023	12.460	13.015
ISV, liters	12.277	12.622	10.992	13.878	9.964	10.056
BV_{out}, liters	0		0.962		1.269	
UV, liters			0.717			
V_{in}, liters	1.095		4.8		1.469	
r_C	0.561		0.569		0.578	
D_-	0.941		0.948		0.949	
F_P	1.000	0.766	1.000	0.658	1.000	0.541
pH	7.431*		7.405*		7.372*	
P_{CO_2}, Torr	39.2*	39.2	39.1*	39.1	41.7*	41.7
Plasma [HCO_3^-], mmol/l	25.55*		23.99*		23.74*	
BE, mmol/l	1.85*		−0.10*		−1.09*	
Total protein, g/l	70†	54	62	41	62	34
Albumin, g/l	44	34			42	23
Plasma lactate, mmol/l	1.4	0.9	0.4	0.6	0.6	0.5

*Corrected for end P_{CO_2}; †assumed normal value. BV, blood volume: estimated from body weight; Hct, hematocrit; RCV, red cell volume; PV, plasma volume; ECV, extracellular volume: estimated 0.2 from body weight; ISV, interstitial volume; BV_{out}, lost blood; UV, urine volume; V_{in}, infused volume; r_C, distribution ratio for bicarbonate between erythrocytes and plasma; D_-, Donnan factor between interstitial fluid and plasma; BE, whole blood base excess; [HCO_3^-], bicarbonate concentration; Hetastarch or HES, hydroxyethyl starch (60 g/l) in 0.9% saline (154 mmol/l).

The characteristic in the clinical study by Rehm et al. (12) was ANH, with the same colloids as in the study by Waters and Bernstein (21), before surgery in two randomized groups of female patients, receiving either 6% HES solution (HES group) or 5% albumin solution (HA group). Because, during ANH, BV before (BV_o) and after hemodilution (BV) is assumed to be the same, all other volumes were estimated as follows: RCV = $BV_o \cdot Hct$; PV = BV_o − RCV; ECV = ECV_o + V_{in} − $BV_{out} \cdot (1 - Hct_{out})$; and ISV = ECV − PV.

With the values from Table 3, pH, plasma [HCO_3^-], BE, and change in (Δ) BE in the different clinical studies after infusion were calculated and compared with reported values. The agreement was good in the Hetastarch group: slight negative change in BE predicted (ΔBE: −1.81 mmol/l) and reported (ΔBE: −1.54 mmol/l); in the saline group: strongly predicted acidosis (ΔBE: −6.48 mmol/l) and reported (ΔBE: −6.61 mmol/l); and in the HES group: moderately predicted acidosis (ΔBE: −2.81 mmol/l) and reported (ΔBE: −2.38 mmol/l) (Table 4). In Table 3, the estimated volumes before and after hemodilution are within the experimental range (plus/minus %variation) of the values determined by Rehm et al. (11, 12) for plasma (±12.9%), erythrocytes (±14.6%), and blood (±11.6%), as well as for estimated total plasma protein (±7.9%) and albumin (±10.6%) concentration. If taking for calculation in the HES group the original values by Rehm et al. (12), instead of the estimated ones before and after hemodilution, the results are similar for pH, 7.322; actual HCO_3^-, 21.14 mmol/l; BE, −4.29 mmol/l; and ΔBE, −3.29 mmol/l. However, it was contradictory in the HA group studied by Waters and Bernstein (21), no agreement between slight changes in BE predicted (ΔBE: −1.83 mmol/l) and reported (ΔBE: +0.64 mmol/l), and by Rehm et al. (12), excellent agreement between moderately predicted acidosis (ΔBE: −2.93 mmol/l) and reported (ΔBE: −2.97 mmol/l). Also, in the Ringer group, studied by Scheingraber et al. (14), there was no agreement: strongly predicted acidosis (ΔBE: −5.81 mmol/l) vs. reported normal BE (ΔBE: −0.48 mmol/l).

In the clinical study by Singbartl et al. (18), a great number of patients (n = 127) who underwent ANH preoperatively were classified according to the mean infused volumes of a colloid solution (Haemaccel): 0, 1, 2, 3, 4, 5, and 5.5 liters. The basic values necessary for prediction of pH, plasma [HCO_3^-], and BE were calculated in the same way as in the study by Rehm et al. (12); however, the final calculations were performed in consecutive steps without P_{CO_2} corrections (0 to 1, 1 to 2, 2 to 3, etc., and not 0 to 1, 0 to 2, 0 to 3, etc.) (Table 5). The BV_o (4.435 liters) before ANH was calculated from the mean body weight (see MATERIALS AND METHODS) and was weighted by the number of the male (n = 49) and female (n = 78) patients. To keep the patients normovolemic, the V_{in} of the colloid was larger than the volume of the replaced blood ($BV_{out} = V_{in}/1.3$) by ANH. In each group, the plasma lactate concentration was also measured and did not change significantly (<1 mmol/l), even under extreme hemodilution. The agreement between predicted and reported values in pH, plasma [HCO_3^-], BE, and ΔBE at the end of ANH is excellent.

DISCUSSION

Based on the dilution concept, nonrespiratory acidosis was predicted for all hypothetical and clinical examples treated in this study: both from dilution with 0.9% saline (simple buffer solutions, whole blood in vitro), and also in whole body from infusion with different colloid (6% HES, 5% HA, polygelatin) or crystalloid solutions (0.9% saline, lactated Ringer). It was also shown that hemodilution cannot be correctly described by simple dilution without taking into account all processes in which HCO_3^- is involved in response to addition or infusion of a diluent. However, it must be emphasized that, for all predictions, additional concentrations of the plasma electrolytes were not necessary.

The algorithm that was derived stepwise for hemodilution in whole body (3-fluid compartment) is the most general. Therefore, the algorithms for dilution of whole blood in vitro, plasma, or simple buffer solutions can be derived if the special limiting conditions are considered. For example, for HCO_3^-/phosphate buffer (1-fluid compartment), *Eq. 14* reduces to $[HCO_3^-(P)] = [HCO_3^-(P)]_{dil} + x(P)$, by setting ISV = 0, RCV = 0, and replacing the HCO_3^- formation term of the plasma proteins by phosphate. For dilution in whole body, the predictions depend on the validity of several assumptions [3-fluid compartment, HCO_3^- distribution functions (r_C, D_-), no HCO_3^- loss in the urine, no metabolic HCO_3^- formation, HCO_3^--free diluents] and on the inaccuracy of the measured or estimated variables. An assumed variance in initial pH (±0.01) and in both initial and final P_{CO_2} (±1.5 Torr), respectively, greatly affect calculated pH (±0.010 and ±0.021), plasma HCO_3^- (±0.50 and ±0.72 mmol/l), and BE (±0.65 and ±0.86 mmol/l), whereas those in estimated volume of blood and ECF are of minor influence. Hence, initial pH and plasma HCO_3^- were corrected for end P_{CO_2} (Tables 3 and 4). The close agreement with reported values in whole body from different clinical studies (Tables 4 and 5) indicates that the observed nonrespiratory acidosis is of dilutional origin, and, where it does not agree (lactated Ringer), it is secondary to other causes and must be diagnosed further. The dilution concept is not

Table 4. *Predicted and reported acid-base values after infusion from different clinical studies*

	After Infusion					
	Predicted	Actual	Predicted	Actual	Predicted	Actual
Clinical study	Waters and Bernstein (21)		Scheingraber et al. (14)		Rehm et al. (12)	
Infused solution	Hetastarch		0.9% saline		6% HES	
pH	7.406±0.010	7.410	7.304±0.010	7.302	7.328±0.011	7.335
P_{CO_2}, Torr	39.2	39.2	39.1	39.1	41.7	41.7
[HCO_3^-], mmol/l	24.12±0.55	24.33	19.02±0.43	18.93	21.44±0.52	21.78
BE, mmol/l	0.04±0.04	0.31	−6.58±0.58	−6.71	−3.90±0.66	−3.78
ΔBE, mmol/l	−1.81±1.01	−1.54	−6.48±0.91	−6.61	−2.81±0.96	−2.38

All estimates of variance are based on assumed variance of initial pH (±0.01) and of initial and final Hb concentration (±0.5 g/dl). ΔBE, difference in base excess before and after infusion.

Table 5. *Dilution in whole body: baseline data and predicted vs. reported acid-base values in patients under extreme acute normovolemic hemodilution*

	Patient Groups Receiving Different Amounts of Infused Volume, liters						
	0	1	2	3	4	5	5.5
Clinical study: Singbartl et al. (18)							
ECV, liters	14.800	15.263	15.694	16.102	16.486	16.862	17.048
BV, liters	4.435	4.435	4.435	4.435	4.435	4.435	4.435
Hct, %	33.0	27.5	24.5	21.4	18.6	19.0	17.8
RCV, liters	1.464	1.218	1.086	0.948	0.825	0.843	0.787
PV, liters	2.971	3.217	3.349	3.487	3.610	3.592	3.648
ISV, liters	11.829	12.046	12.345	12.615	12.876	13.270	13.400
BV_{out}, liters	0	0.769	0.769	0.769	0.769	0.769	0.385
V_{in}, liters	0	1	1	1	1	1	0.5
r_C	0.562	0.576	0.579	0.586	0.593	0.590	0.604
F_P	1.000	0.768	0.857	0.838	0.840	1.028	0.920
D_-	0.948	0.961	0.967	0.972	0.977	0.976	0.979
P_{CO_2}, Torr	40.2	42.9	42.1	42.7	43.2	41.2	45.4
Predicted values							
pH	7.430	7.379	7.368	7.341	7.316	7.328	7.278
Plasma [HCO_3^-], mmol/l	26.13	24.82	23.70	22.62	21.59	21.18	20.81
BE, mmol/l	2.27	0.05	−1.15	−2.59	−3.94	−4.10	−5.29
ΔBE, mmol/l	0	−2.22	−3.42	−4.86	−6.21	−6.37	−7.56
Measured values							
pH	7.43	7.38	7.36	7.34	7.31	7.32	7.28
Plasma [HCO_3^-], mmol/l	26.13	24.85	23.29	22.56	21.30	20.79	20.89
BE, mmol/l	2.27	0.09	−1.66	−2.67	−4.31	−4.60	−5.19
ΔBE, mmol/l	0	−2.18	−3.93	−4.94	−6.58	−6.87	−7.46
Plasma lactate, mmol/l	0.84	0.69	0.68	0.65	0.58	0.76	0.57

Colloid solution (Haemaccel) contained 35 g/l polygelatin, 145 mmol/l sodium, 5.1 mmol/l potassium, 6.25 mmol/l calcium, and 145 mmol/l chloride. No. of patients = 127; mean age = 65 ± 13 yr; mean body weight = 74 ± 13 kg; total plasma protein = 62 g/l assumed. ECV is estimated 0.2 from body weight; Hct is calculated from measured Hb (g/dl); BV_{out} is estimated blood loss (V_{in}/1.3); V_{in}, infused volume; ΔBE is before and after hemodilution.

restricted to the HCO_3^-. If the Stewart approach is used for prediction of the dependent variables of pH or HCO_3^- after hemodilution, the SID must also be predicted from dilution. This, however, requires several ions (sodium, potassium, chloride, lactate), in contrast to the revised dilution concept, in which electrolytes other than HCO_3^- are not necessary.

Dilutional acidosis. For whole blood in vitro, the extent of dilutional acidosis can be predicted from volume expansion, with 0.9% saline in the whole range from initial (15.2 g/dl) to infinite dilution. In Fig. 1, this is expressed in a plot of plasma [HCO_3^-] (mmol/l) vs. relative Hb (%) after hemodilution at constant P_{CO_2} = 40 Torr. The actual concentration (first curve) is the sum of the decreased HCO_3^- from plasma dilution (second curve), plus the increment of HCO_3^- formation from the plasma proteins (fourth curve), plus the increment of HCO_3^- formation from Hb and transfer from the erythrocytes (third curve). The contributions from the plasma proteins are negligible (<1 mmol/l); only those of the erythrocytes with a broad maximum diminish the strong acidosis from pure plasma dilution. For example, in half-diluted blood (1:2), the predicted [HCO_3^-] is 14.38 mmol/l, consisting of 8.56 mmol/l from plasma dilution (59.5%), 5.24 mmol/l from transfer from the erythrocytes (36.4%), and 0.58 mmol/l from the plasma proteins (4.0%). The percent decrease in plasma HCO_3^- (40.7%) agrees with the extrapolated value (39.8%), obtained from an empirical formula for whole blood by Garella et al. (4). Also, the predicted BE (−13.2 mmol/l) is comparable to a recent value (−11.0 ± 2.2 mmol/l) from dilution of blood with 0.9% saline (BE = 1.4506·[Hb] − 22.47) (8).

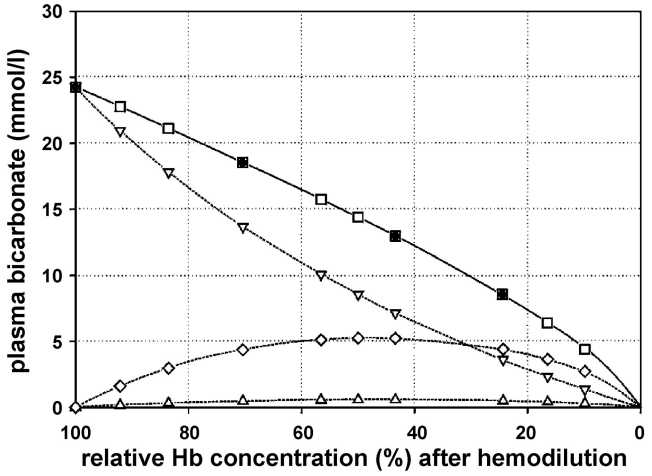

Fig. 1. Plasma bicarbonate (HCO_3^-; mmol/l) vs. relative Hb (%) after hemodilution with 0.9% saline in vitro. Comparison is shown of predicted (□) and reported (■) values (23) of the actual concentration (*top* curve), and the calculated contributions from plasma dilution (▽), plasma proteins (△), and erythrocytes (◇).

In a similar plot, acidosis from hemodilution in whole body under extreme ANH with colloid solution under normocapnic conditions is demonstrated in Fig. 2. The points on the fourth curve describe the decreased plasma [HCO_3^-] from pure plasma dilution, to which the negligible fractions from the plasma proteins (<1 mmol/l) are successively added, from the erythrocytes (1.2–2.2 mmol/l), and from the ISF (3.3–7.2 mmol/l). In the range of hemodilution (relative Hb, 100–50%), no maxima can be observed in the contributions from the erythrocytes or from the ISF. The BE is negative for all groups, and the changes in BE under extreme hemodilution ([Hb] = 5.93 g/dl), predicted (−7.56 mmol/l) and reported (−7.46 mmol/l), obviously were not caused by lactic acidosis from oxygen deficit, but from dilution by volume replacement. The corresponding decrease in plasma

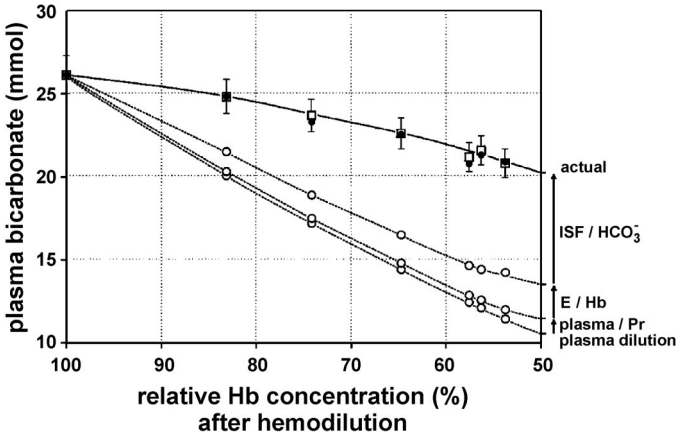

Fig. 2. Plasma HCO_3^- concentration (mmol/l) vs. relative Hb (%) after acute normovolemic hemodilution in different patient groups. Comparison is shown of predicted (□) and reported (■) values (18) of the actual HCO_3^- (*top* curve), composed of the calculated HCO_3^- (○) from plasma dilution, plus the increments from the plasma proteins (Pr), the erythrocytes (E), and the interstitial fluid (ISF) with corresponding buffers.

HCO_3^- (20.81 mmol/l) with respect to the baseline value (26.13 mmol/l), predicted (20.4%) and reported (20.1%), is in good agreement with the calculated result (19.7%) from the empirical formula by Garella et al. (4) in dogs.

Infusion solutions and prevention of dilutional acidosis. When dilutional acidosis was verified by experimental evidence in dogs from isotonic solutions, irrespective of whether they contained chloride or not (1), it was also demonstrated that this could be prevented by infusion of balanced HCO_3^- solution (in mmol/l: 140 Na^+, 2.4 K^+, 112.5 Cl^-, and 30 HCO_3^-) instead of 0.9% saline (16). The acid-base effects observable from infusion on whole body greatly depend on composition of the administered fluid, as well as on its volume and rate. Hence, it is surprising that infusion solutions are badly characterized with respect to their actual acid-base properties in the body. In recent time, two attempts have been made: the one proposed by Zander (22), who transferred the conventional BE concept to infusion solutions, including also metabolic effects from HCO_3^- precursors such as lactate, citrate, or acetate by an additional term, called the potential BE; the other proposed by Morgan et al. (8), who used the SID concept. By the latter declaration, however, the clinical implications are not always immediately comprehensible if the $[HCO_3^-]$ is not explicitly given. This is the case, e.g., in hypoproteinemic alkalosis, which is explained by a decrease in the plasma proteins, and the in vitro data of human blood from Rossing et al. (13) have been frequently cited. In the plasmalike diluent (in mmol/l: 143 Na^+, 3.9 K^+, 108 Cl^-, 39 total CO_2), the SID ($Na + K - Cl$) is 38.9 mmol/l and equals approximately the sum of the HCO_3^- + the proteinate concentration, if present in the solution. To a clinician, however, who is aware of 38.9 mmol/l of HCO_3^- in the solution, alkalosis is not surprising.

In the chosen clinical studies, all infusion solutions contained high-sodium (>142 mmol/l) and high-chloride (>102 mmol/l) concentrations, except for lactated Ringer solution (in mmol/l: 130 Na^+, 112 Cl^-, and 27 lactate) by Scheingraber et al. (14) and 5% albumin solution by Waters and Bernstein (21), suspected to contain HCO_3^- of unknown amounts (in mmol/l: 150 Na^+, 93 Cl^-, and <50 HCO_3^-). For the latter two solutions, however, acidosis was predicted, in contrast to the reported normal acid-base state. These obvious discrepancies are good examples, demonstrating how the dilution concept can successfully be applied. Because in the organism HCO_3^- can be metabolically generated from lactate, lactated Ringer solution is only apparently HCO_3^- free. Analyzing the acid-base state before and after infusion with lactated Ringer solution, the difference in ΔBE between actual (−0.48) and predicted (−5.81) is +5.33 mmol/l. Hence, the amount of base to compensate for dilutional acidosis in the Ringer group must be 82.5 mmol [= 0.2·BE (mmol/l)·body weight (kg)]. From a simple balance of converted and total infused lactate (5.2 l × 27 mmol/l = 140 mmol) at the end of 2 h, the concentration of lactate in the ECF (19.0 liter) is ~3.1 mmol/l, close to the measured plasma concentration of 2.0 mmol/l. Hence, iatrogenically caused dilutional acidosis was compensated by induced alkalinizing hepatic metabolism, which is the strategy of this widely used solution in preventing nonrespiratory acidosis. However, most solutions for use in clinical practice are not physiological (high chloride; no HCO_3^-) and are often a compromise due to the manufacturing conditions (sterility, stability, costs). This must lead to additional acid-base effects (dilutional acidosis, rebound alkalosis from metabolizable anions), if such solutions are administered into patients in large amounts. In the case of dilutional acidosis caused from HCO_3^--free solutions, irrespective of whether they contain chloride or not, measured plasma chloride concentration may be used for additional characterization as hyper- or hypochloremic.

APPENDIX

Equations for Calculation of Formed HCO_3^- from Phosphate Buffer at Constant Pco_2

$[HCO_3^-]$ as a function of pH, if $x = [HCO_3^-]_{formed}$, is substituted from *Eq. 5* into *Eq. 4*:

$$[HCO_3^-] = f_1(pH) = F_{dil}\left([HCO_3^-]_o + \frac{[HPO_4^{2-}]_o - [H_2PO_4^-]_o \times 10^{pH-6.8}}{1 + 10^{pH-6.8}}\right) \quad (A1)$$

Equations for Calculation of Formed HCO_3^- from Plasma Proteins and Oxygenated Hb

Equations 8 and *9* are derived from the titration curves of the plasma proteins (g/l), [Pr(P)], and of the oxygenated Hb in the erythrocytes of normal concentration, MCHC = 334 g or 20.7 mmol/l heme monomer by differentiation for pH, according to the following equations (20):

$$[Pr^-(P)] = [Pr(P)] \times [0.2413 + 0.104 \times (pH - pH_o)] \quad (A2)$$

where $[Pr^-(P)]$ is the concentration of proteinate (meq/l), and

$$[HbO_2^-(E)] = MCHC \times [10.625 \times pH(E) - 0.5 \times pH^2(E) - 48.48] \quad (A3)$$

Because, in the erythrocytes, $pH(E) = 7.19 + 0.77 \times (pH - 7.40)$, differentiation for pH in *Eq. A3* yields:

$$\Delta[HbO_2^-(E)]/\Delta pH = \{\Delta[HbO_2^-(E)/\Delta pH(E)\} \times [\Delta pH(E)/\Delta pH] = MCHC \times [10.625 - pH(E)] \times 0.77 \quad (A4)$$

Substituting in *Eq. A4* for pH(E) and inserting MCHC = 20.7 mmol/l, the change in plasma pH from initial pH_o to final pH yields *Eq. 9*, but without the negative sign.

Complete Equations for ΔC_E of whole blood in vitro

From combination of *Eqs. 10* and *11* and rearranging, $\Delta C_E(1)$ is explicitly given:

$$\Delta C_E(1) = \frac{[HCO_3^-(E)]_o - r_C \times \left([HCO_3^-(P)]_{dil} - (pH - pH_o) \times \left\{ 0.104 \times [Pr(P)]_{dil} + \frac{RCV}{PV} \times (145.571 - 12.273 \times pH) \right\} \right)}{1 + \frac{RCV}{PV} \times r_C}$$

All quantities are known from the baseline data and as a function of plasma pH. The empirical relationship for the distribution ratio of HCO_3^- as a function of pH is taken from Siggaard-Andersen (17) and was linearized: $r_C = 0.57 - 0.28 \times (pH - 7.4) = 2.642 - 0.28 \times pH$.

Similarly, introduction of *Eq. 11* into the HH *Eq. 12* yields $\Delta C_E(2)$:

$$\Delta C_E(2) = \frac{PV}{RCV} \times \left(0.0304 \times P_{CO_2} \times 10^{pH-6.1} - [HCO_3^-(P)]_{dil} + (pH - pH_o) \times \left\{ 0.104 \times [Pr(P)]_{dil} + \frac{RCV}{PV} \times (145.571 - 12.273 \times pH) \right\} \right)$$

In all calculations, the ratio RCV/PV is replaced by the hematocrit: Hct/(1 − Hct).

Complete Equations for ΔC_E in Whole Body

From distribution of HCO_3^- between ISF and plasma (P):

$$[HCO_3^-(P)] = D_- \times \{F_{ISF} \times [HCO_3^-(ISF)]_o - \Delta C_{ISF}\} \quad (A5)$$
$$= F_{ISF} \times [HCO_3^-(P)]_o - D_- \times \Delta C_{ISF}$$

where $[HCO_3^-]_o$ in ISF is calculated from initial concentration in plasma: $[HCO_3^-(ISF)]_o = [HCO_3^-(P)]_o/D_-$.

Hence from *Eqs. 13* and *14*, ΔC_{ISF} can be isolated:

$$\Delta C_{ISF} = \frac{F_{ISF} \times [HCO_3^-(P)]_o - [HCO_3^-(P)]_{dil} - x(P) - [x(E) + \Delta C_E] \times \frac{RCV}{PV}}{\left(\frac{ISV}{PV} + D_- \right)} \quad (A6)$$

From distribution of HCO_3^- between erythrocytes (E) and plasma (P), and substituting for ΔC_{ISF} into *Eq. 14*:

$$\Delta C_E(1) = \frac{[HCO_3^-(E)]_o - r_C \times \left[F_{ISF} \times \left\{ \frac{[HCO_3^-(P)]_o}{1 + \frac{PV}{ISV} \times D_-} \right\} + \left\{ [HCO_3^-(P)]_{dil} + x(P) + x(E) \times \frac{RCV}{PV} \right\} \times \left(1 - \frac{1}{1 + \frac{PV}{ISV} \times D_-} \right) \right]}{1 + r_C \times \frac{RCV}{PV} \times \left(1 - \frac{1}{1 + \frac{PV}{ISV} \times D_-} \right)}$$

and from the HH *Eq. 12* :

$$\Delta C_E(2) = \frac{PV \times \left[sCO_2 \times P_{CO_2} \times 10^{pH-6.1} - F_{ISF} \times \left\{ \frac{[HCO_3^-(P)]_o}{1 + \frac{PV}{ISV} \times D_-} \right\} - \left\{ [HCO_3^-(P)]_{dil} + x(P) + x(E) \times \frac{RCV}{PV} \right\} \times \left(1 - \frac{1}{1 + \frac{PV}{ISV} \times D_-} \right) \right]}{RCV \times \left(1 - \frac{1}{1 + \frac{PV}{ISV} \times D_-} \right)}$$

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