EASY WAY TO UNDERSTAND STEWART'S ACID-BASE

FROM "SALINE" TO MORE "PHYSIOLOGIC" FLUID

Yohanes WH George, MD

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NOTICE

Medicine is an ever- changing field. Because of new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate, Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended standard of administration. It is the responsibility of the licensed prescriber, relying on experience and knowledge of the patient, to determine the best treatment of each individual patient. Neither the publisher nor the author assume any liability for any injury ang/or damage to persons or property arising from this publication.

ISBN. ....

Contents

Dedication

To my great teacher and mentor;

In memoriam

DR. Iqbal Mustafa, MD. FCCM

the pioneer of the modern critical care medicine in Indonesia,

Head of Intensive Care Unit Harapan Kita Hospital (1992-2004),

Jakarta- Indonesia

Foreword

In critical care and anesthesia medicine, fluid administration is a key element of resuscitation. Currently, there are still controversies regarding fluid resuscitation strategies, both on 'balanced fluid' strategy, known as 'goal-directed therapy', and from 'fluid option' point of view, which is about fluid type selection. In terms of 'fluid option', controversial debate about crystalloid and colloid has lasted for a long time and is no more a special concern. Selection of resuscitation fluids based on their effects on acid-base balance of the body is currently a particular concern. Evidences suggest that saline use in fluid resuscitation causes hyperchloremic acidosis, therefore nonsaline-based fluid, also known as 'balanced fluid', is currently invented to avoid acidosis effect.

The mechanism of acidosis following saline administration is based on acid-base balance method by Stewart, that is also called quantitative method or physicochemical approach. Unfortunately, this theory is not widely understood despite the fact that it has been known for quite some time (since 1978) and is being accepted slowly in critical care and anesthesia medicine, which is partly caused by its complexity and being not easily understood.

The Department of Anesthesia of RSCM - FKUI finds that this handbook of "EASY WAY TO UNDERSTAND STEWART'S ACID-BASE" is very useful and it will hopefully simplify the understanding of acid-base balance disturbance mechanism based on Stewart's method for doctors, especially anesthesiologists and doctors who work in emergency departments and critical care units, which will eventually improve the safety and quality of resuscitation fluids selection. We send our special thanks to dr. Yohanes WH George who made this handbook schematic, practical and easy to understand.

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Head of Department of Anesthesiology and Intensive Care Unit
Cipto Mangunkusumo Hospital, Medical Faculty, University of Indonesia

Preface

Understanding the chemistry of water and hydrogen ions is an important part of understanding the living system because hydrogen ions participate in so many reactions. One interesting facet of human homeostasis is the tight control of hydrogen ion concentration, [H+]. As metabolism creates about 300 liters of carbon dioxide each day, and as we also consume about several hundred mEq of strong acids and bases in the same period, it is remarkable that the biochemical and feedback mechanism can maintain [H+] between 30 and 150 nanoEq/liter.

Appreciation of the physics and chemistry involved in the regulatory process is essential for all life scientists, especially physiologists. Many physiology textbooks start the discussion of acid-base equilibrium by defining pH , which immediately followed by the Henderson-Hasselbalch equation.

Attention has recently shifted to a *quantitative* physicochemical approach to acid-base physiology. Many of the generally accepted concepts of hydrogen ion behaviour are viewed differently. This analysis, introduced by Peter Stewart in 1978, provides a chemical insight into the complex chemical equilibrium system known as acid-base balance.

The impact of Stewart's analysis has been slow, but there has been a recent resurgence in interest, particularly as this approach provides explanations for several areas which are otherwise difficult to understand (e.g. dilutional acidosis, acid-base disorders related to changes in plasma albumin concentration).

Undoubtedly, the physicochemical approach will become more important in the future and this brief review provides an introduction to this method.

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STEWART'S APPROACH IN BRIEF

- **GENERAL PRINCIPLES OF STEWART'S APPROACH**
  - Electroneutrality. In aqueous solutions in any compartment, the sum of all the positively charged ions must equal to the sum of all the negatively charged ions.
  - The dissociation equilibria of all incompletely dissociated substances, as derived from the law of mass action, must be satisfied at all times.
  - Conservation of mass, the amount of a substance remains constant unless it is added, removed, generated or destroyed. The relevance is that the total concentration of an incompletely dissociated substance is the sum of concentrations of its dissociated and undissociated forms.

Stewart PA. How to understand acid-base. A quantitative acid-base primer for biology and medicine. Elsevier 1981

Mathematical analysis

- The physico-chemical acid-base approach (Stewart's approach) is different from the conventional approach based on the Henderson-Hasselbalch equation, and requires a new way of approaching acid-base problems.
- In Stewart approach, the $[H^+]$ is determined by the composition of electrolytes and PCO2 of the solution.
- Mathematical analysis shows that it is not absolute concentrations of almost totally dissociated ("strong") ions that influence hydrogen ion concentration, but the difference between the activities of these strong ions (This "strong ion difference" is commonly abbreviated "[SID]").

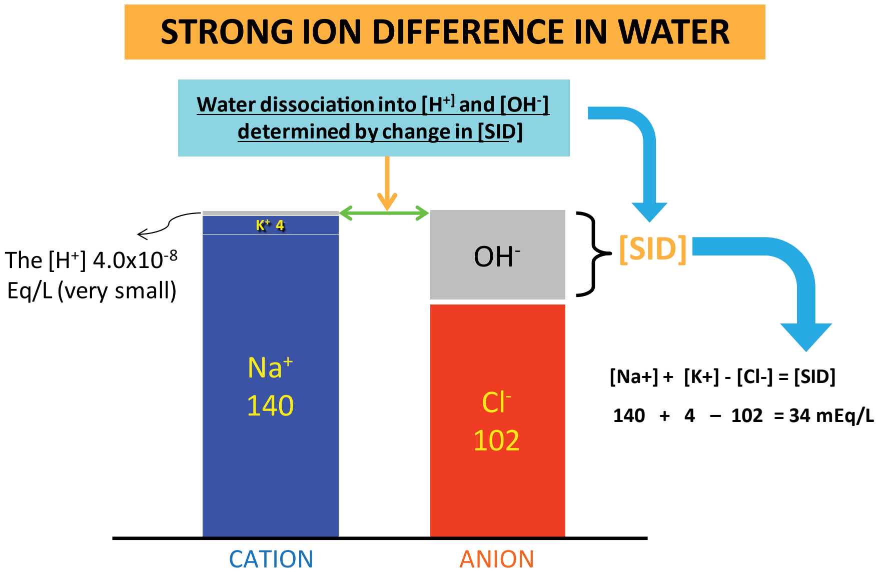
Stewart PA. How to understand acid-base. A quantitative acid-base primer for biology and medicine. Elsevier 1981

STRONG ION DIFFERENCE

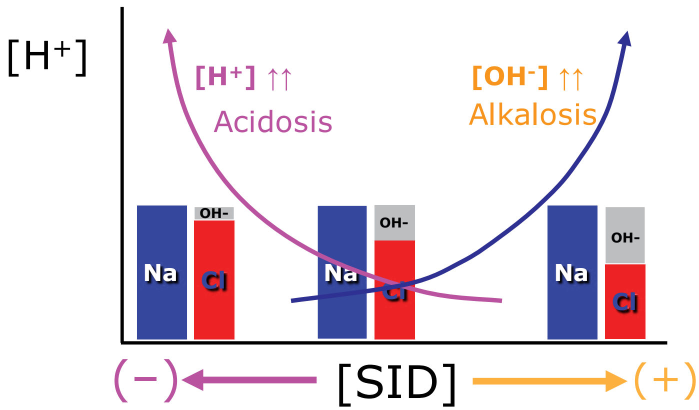
- **DEFINITION:**
  - The strong ion difference is the charge imbalance of the strong ions. In detail, the strong ion difference is the sum of the concentration of the strong base cations, less the sum of the concentrations of the strong acid anions.
  - Strong electrolytes are those which are fully dissociated in aqueous solution, such as the cation sodium (Na^+), or the anion chloride (Cl^-). **BECAUSE STRONG IONS ARE ALWAYS DISSOCIATED, THEY DO NOT PARTICIPATE IN CHEMICAL REACTIONS (UNMETABOLIZABLE IONS)**. Their only role in acid-base chemistry is through the **ELECTRONEUTRALITY** relationship

Stewart PA. How to understand acid-base. A quantitative acid-base primer for biology and medicine. Elsevier 1981

THE GAMBLEGRAM



STRONG ION DIFFERENCE IN WATER

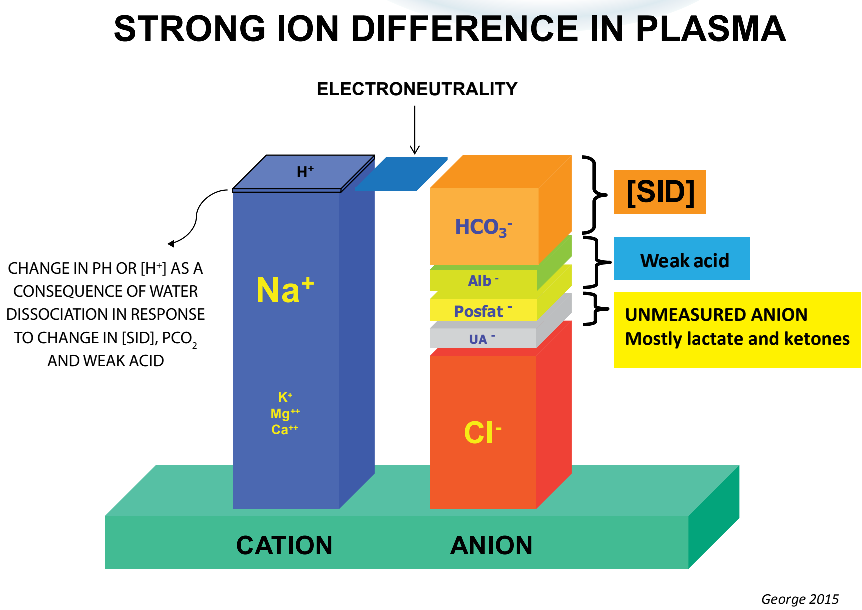


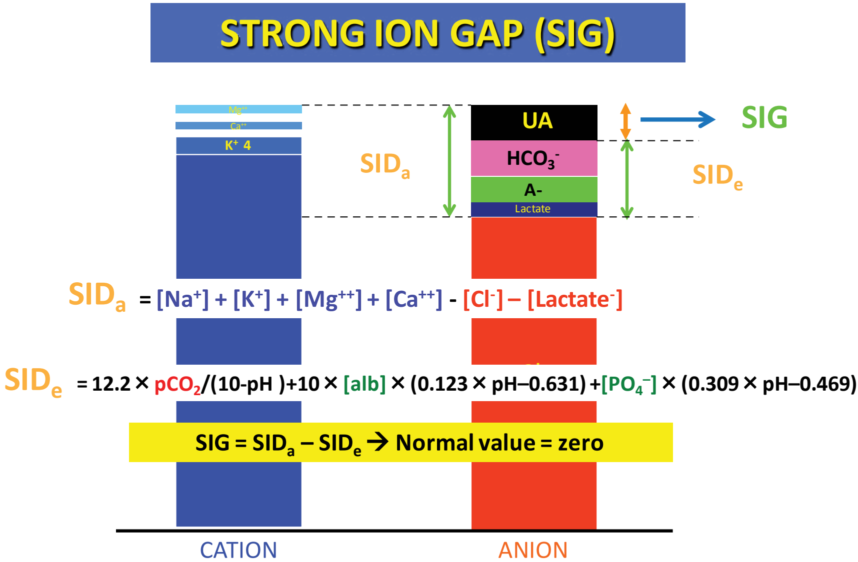
THE RELATIONSHIP BETWEEN [SID] AND pH/[H+]

STRONG ION DIFFERENCE IN PLASMA

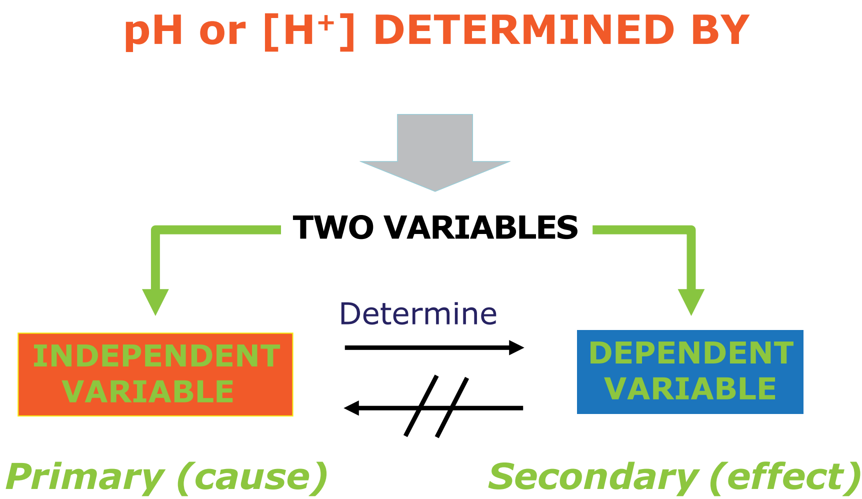
BIOCHEMISTRY OF AQUEOUS SOLUTIONS

1. Virtually all solutions in human biology contain water and aqueous solutions provide a virtually inexhaustible source of $[H^+]$
2. In these solutions, $[H^+]$ concentration is determined by the dissociation of water into H^+ and OH^- ions
3. Changes in $[H^+]$ concentration or pH occur **NOT** as a result of how much $[H^+]$ is added or removed **BUT** as a consequence of water dissociation in response to change in **[SID], PCO_2** and **weak acid**





Kellum JA, Kramer DJ, Pinsky MR: Strong ion gap: A methodology for exploring unexplained anions. *J Crit Care* 1995,10:51--55.



INDEPENDENT VARIABLES

- CO_2 → pCO_2
  Controlled by the respiratory system
- STRONG ION DIFFERENCE → SID
  The electrolyte composition of the blood (controlled by the kidney)
- WEAK ACID → A_{tot}
  Weak Acid, The protein concentration (controlled by the liver and metabolic state)

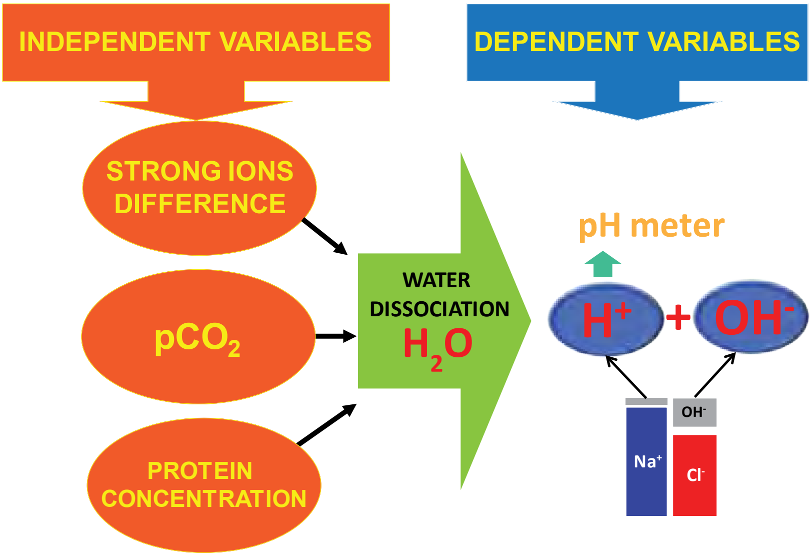
EVERY CHANGE OF THESE VARIABLE WILL CHANGE THE pH

DEPENDENT VARIABLES

- H^+
- OH^-
- $CO_3^{=}$
- A^-
- AH
- HCO_3^-

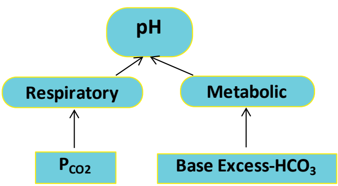
IF THESE VARIABLE CHANGE, THE INDEPENDENT VARIABLES MUST HAVE CHANGED

THE PRACTICAL POINT



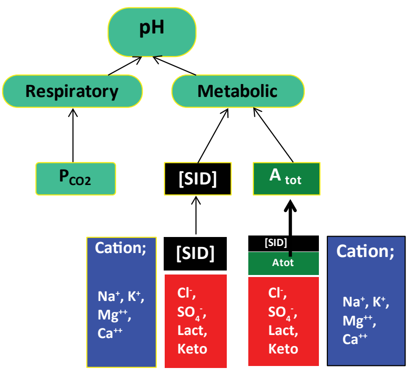
THE DIFFERENCE

Henderson-Hasselbalch



Determinants of plasma pH, as assessed by the H-H. Base excess and standard HCO3- determine the metabolic component of plasma pH

Stewart's Approach



Determinants of plasma pH, at 37^{0}C, as assessed by the Strong Ion Difference [SID] model of Stewart. [SID^+] and [A_{tot}] determine the metabolic component of plasma pH

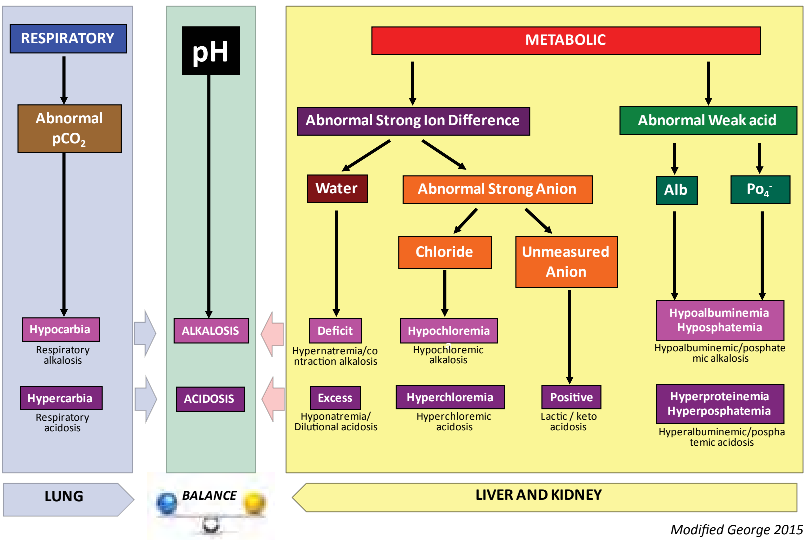
George 2015

THE DIFFERENCE

- The Stewart approach emphasizes mathematically independent and dependent variables.
- Actually, HCO_3- and H^+ ions represent the effects rather than the causes of acid-base derangements.

CLASSIFICATION OF PRIMARY ACID BASE DISTURBANCE

Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 2000 Dec;162(6):2246-51



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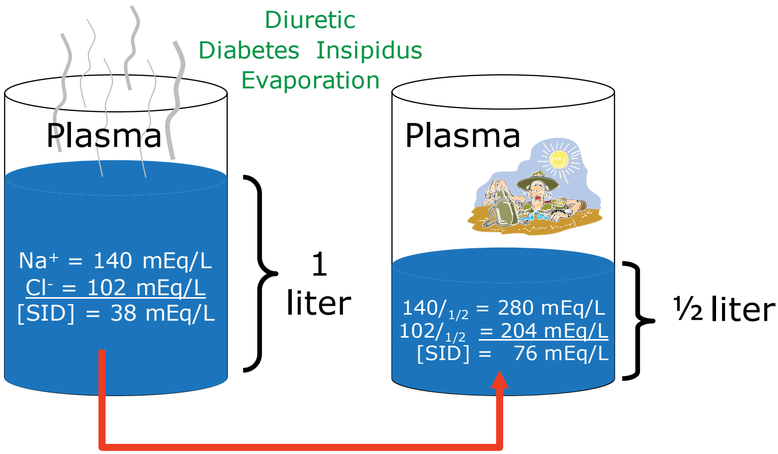
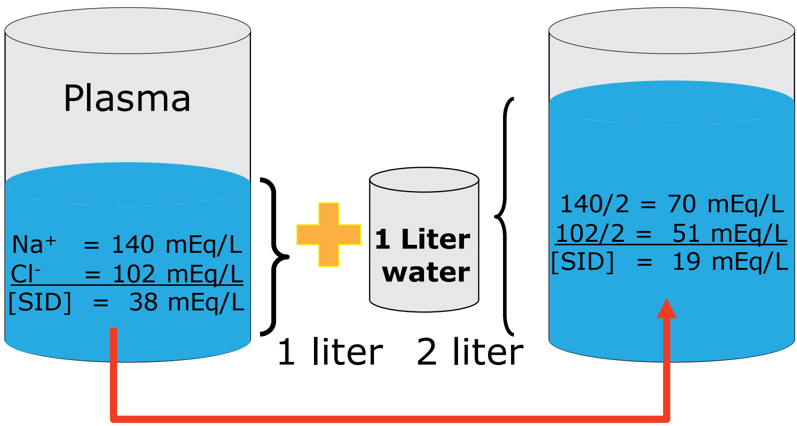
WATER DEFICIT



[SID] : 38 → 76 = alkalosis

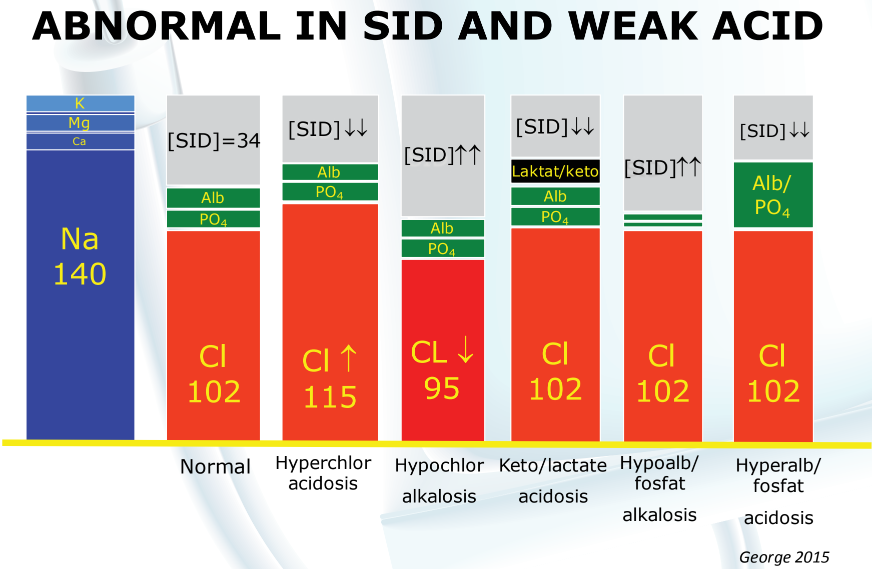
CONTRACTION ALKALOSIS

WATER EXCESS



[SID] : 38 → 19 = Acidosis

DILUTIONAL ACIDOSIS



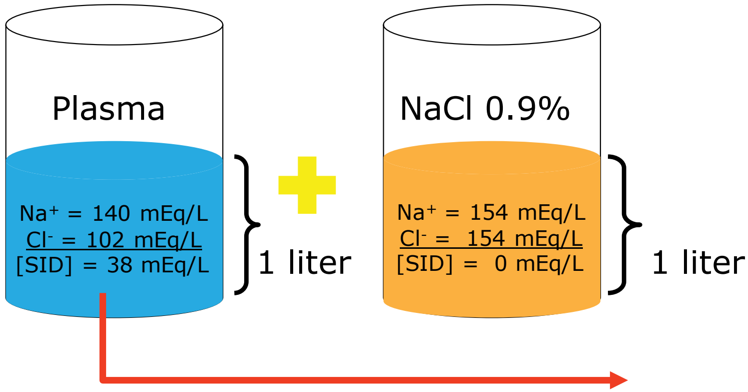
THE EFFECT OF SALINE AND BALANCED FLUID FROM THE STEWART'S PERSPECTIVE

Stewart's approach not only explains fluid induced acid–base phenomena but also provides a framework for the design of fluids for specific acid–base effects

simple analogy

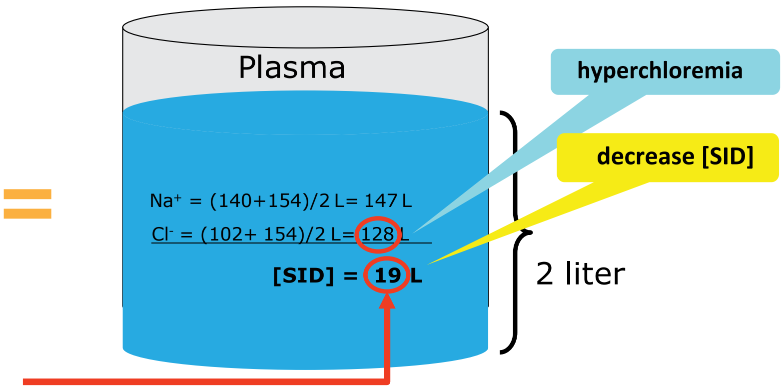
How does saline cause acidosis?

PLASMA + Saline 0.9%



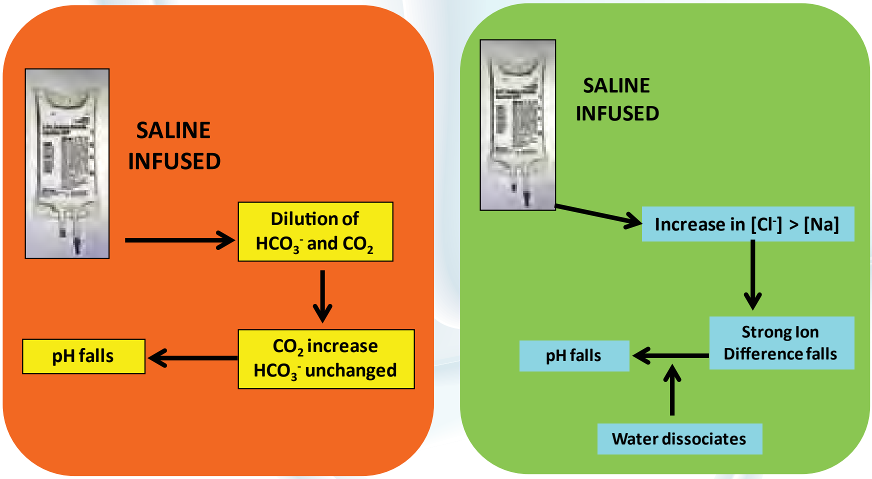
[SID] : 38 → normal pH

SALINE CAUSE ACIDOSIS BY DECREASING [SID] DUE TO THE HYPERCHLOREMIC



[SID] : 19↓ → pH↓ → More acidosis

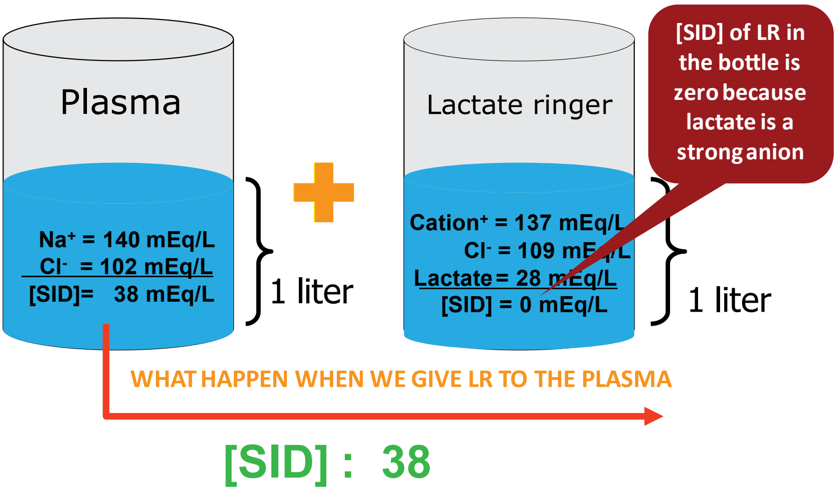
THE DIFFERENCES BETWEEN H-H AND STEWART'S APPROACH IN EXPLAINING ACIDOSIS FOLLOWING INFUSION OF SALINE



D.A Story, Critical Care and Resuscitation 1999; 1:151-156

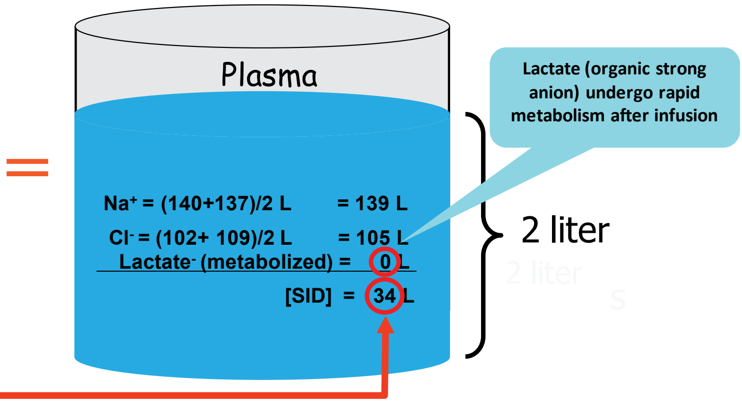
simple analogy

PLASMA + LACTATE RINGER



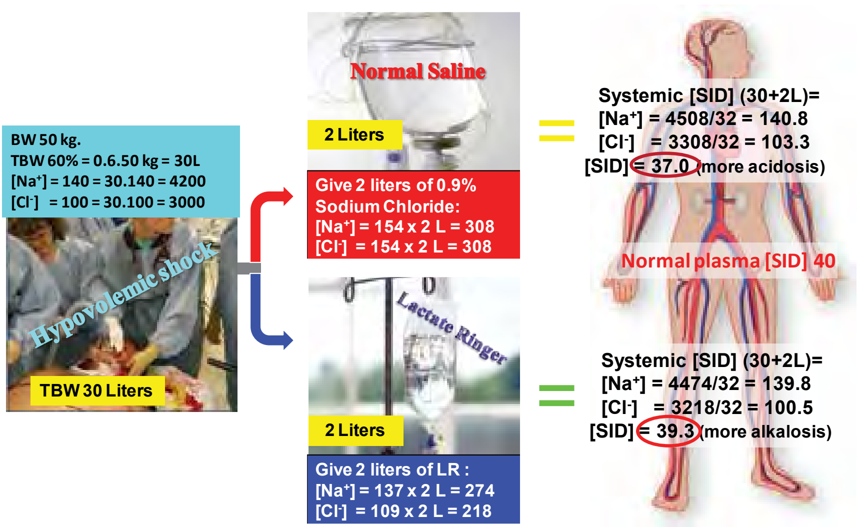
simple analogy

[SID] CLOSE TO NORMAL AFTER LACTATE RINGER INFUSION



[SID] become 34 → plasma pH become more alkalosis than plasma pH after Saline infusion

SALINE INFUSION CAUSE MORE ACIDOSIS THAN LACTATE RINGER



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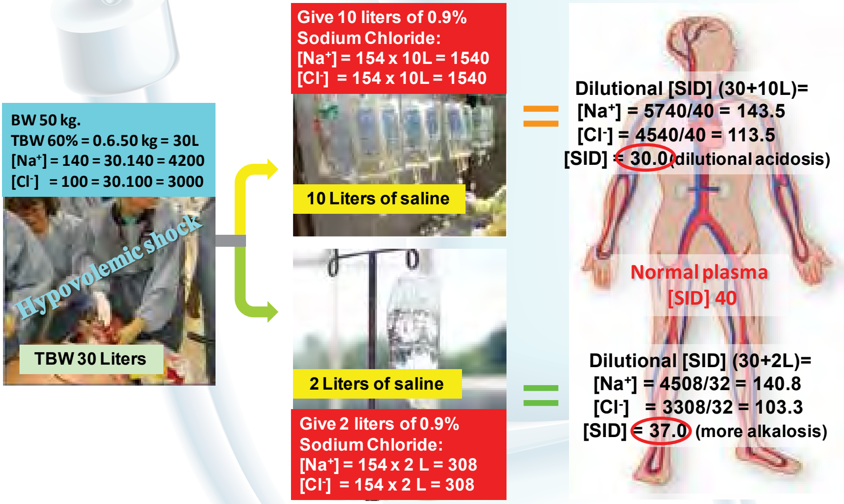
LARGE INFUSION SALINE CAUSE MORE ACIDOSIS



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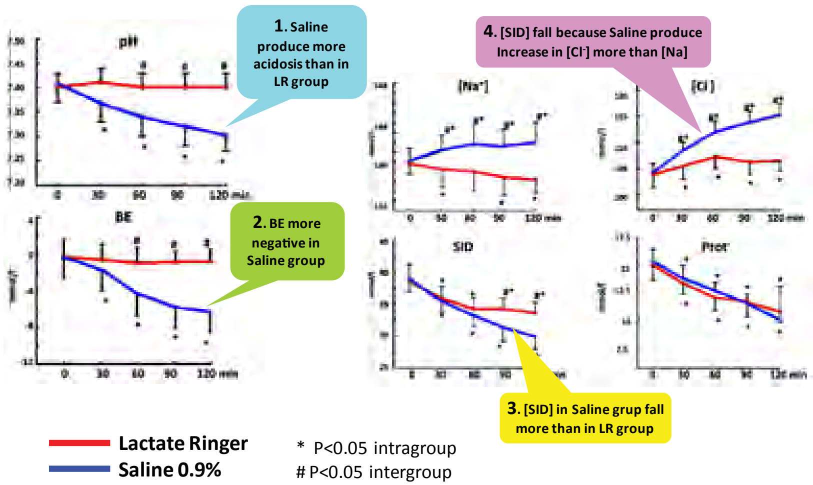
RAPID SALINE INFUSION PRODUCES HYPERCHLOREMIC ACIDOSIS



Scheingraber S, Rehm M, Rapid Saline Infusion Produces Hyperchloremic Acidosis in Patients Undergoing Gynecologic Surgery. Anesthesiology 1999; 90:1247–9

DESIGNING 'BALANCED' CRYSTALLOIDS

- **Large volumes of intravenous saline tend to cause a metabolic acidosis**
- **To counteract this side effect, a number of commercial crystalloids have been designed to be more 'physiologic' or 'balanced'**
- **They contain stable organic anions such as lactate, gluconate, malate and acetate (metabolizable anion)**

BALANCED CRYSTALLOID

Table 1. Three 'balanced' salt solutions (electrolyte concentrations in mmol/L)

	Hartmann's[a]	Plasmalyte[a]	Plasmalyte-R[a]
Sodium	129	140	140
Chloride	109	98	103
Potassium	5	5	10
Calcium	2		5
Magnesium		1.5	3
Lactate	29		8
Acetate		27	47
Gluconate		23	
Effective SID[b]	27	50	53

SID = strong ion difference

[b]SID values are in mEq/L, and assume stable plasma lactate concentrations of 2 mmol/L.

Rapid metabolize after/during infusion

Zero [SID] before infusion

[SID] 27 after infusion

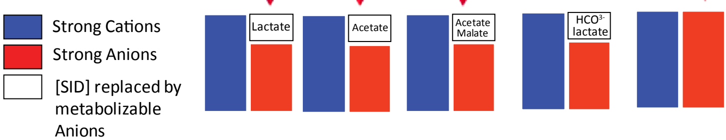
Balanced crystalloid is a solution who have zero [SID] before infusion and have an effective [SID] after the metabolizable anion was metabolized

DESIGNING 'BALANCED' CRYSTALLOIDS

- Balanced crystalloids thus must have a [SID] lower than plasma [SID] but higher than zero (about 24mEq/) to counteract the progressive A_{TOT} dilutional alkalosis during rapid infusion
- In other words, Saline can be 'balanced' by replacing 24mEq/l of Cl^- with various organic metabolizable anions such as Lactate, Malate, Acetate, Gluconate and Citrate as weak ion surrogates
- These metabolizable anions underwent rapid metabolized in the plasma after infusion resulting only small increase the plasma Cl- and then small change in plasma [SID]

THE [SID] OF BALANCED CRYSTALLOID, PLASMA AND SALINE

[mmol/l]	RINGER LACTATE	RINGER ACETATE	RINGER FUNDIN	PLASMA	SALINE	
Na^+	130	130	145	142	154	Strong Cations
K^+	4	5	4	4.5		
Ca^{2+}	2.7	1	2.5	2.5		
Mg^{2+}	1	1	1	0.85		
Cl^-	109	112	127	103	154	Strong Anions
HCO_3^-				24	Zero[SID]	SID replaced by metabolizable Anions except in saline
$Lactate^-$	28	--	--	1.5		
$Acetate^-$	—	27	24			
$Malate^{2-}$	...	--	5			



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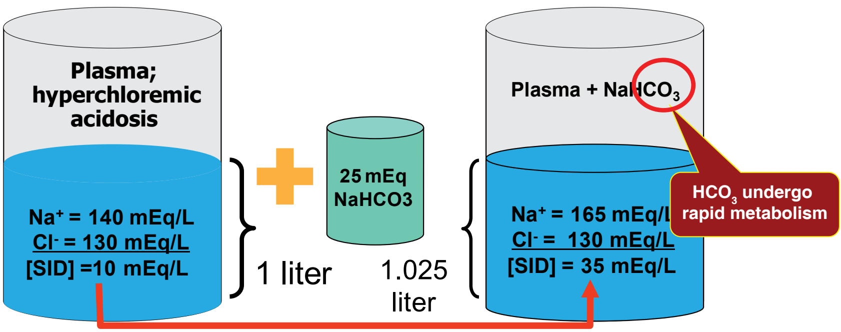
DESIGNING 'BALANCED' CRYSTALLOIDS

- The principles laid down by the late Peter Stewart have transformed our ability to understand and predict the acid–base effects of fluids for infusion
- Designing fluids for specific acid–base outcomes is now much more a science than an art

simple analogy

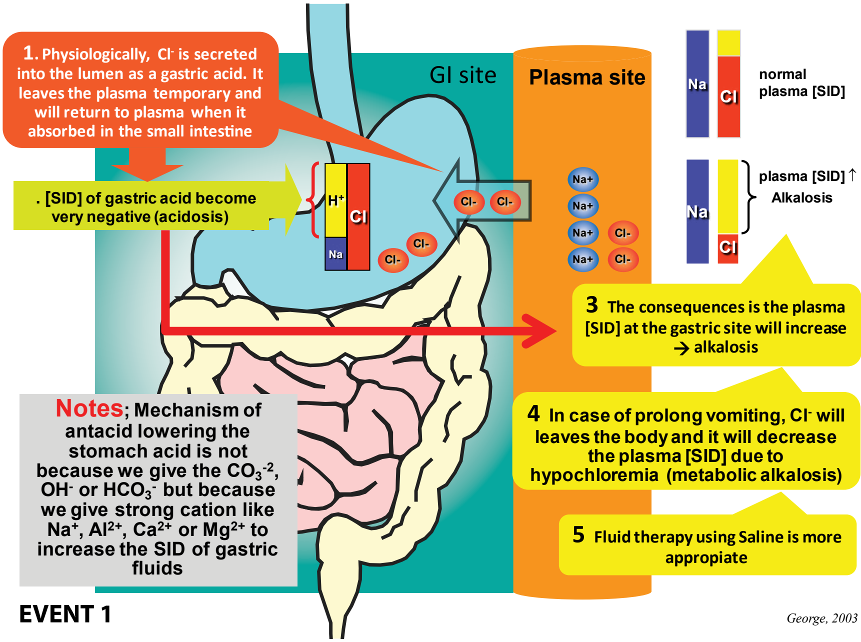
How does bicarbonate increase the pH?



The [SID]↑ : from 10 to 35 : → Alkalosis, pH back to normal → but the mechanisme not because we give the bicarbonate but we give Sodium without strong anion like Chloride, so the [SID]↑ → alkalosis

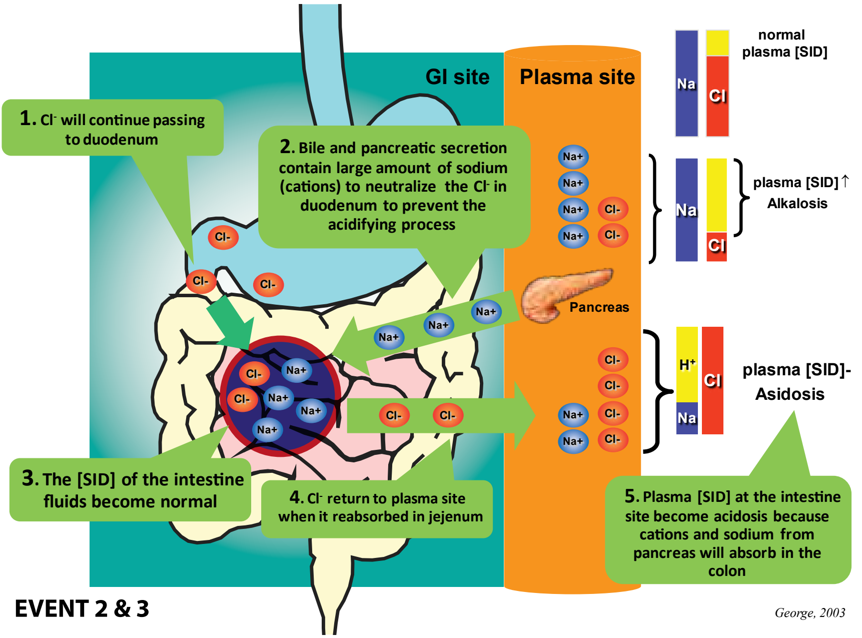
SERIES OF EVENT OF ELECTROLYTE AND ACID-BASE REGULATION IN THE GI TRACT

- **The GI tract is important in acid-base balance because it deals directly with strong ions. It does so differently in different regions along its length, so its useful to consider four separate parts that are quantitatively important in their effects on plasma [SID]**
- **There are four important parts (region);**
    - **Stomach (Event 1)**
    - **Pancreas (Event 2)**
    - **Duodenum (small intestine) (event 3)**
    - **Colon (large intestine) (event 4)**



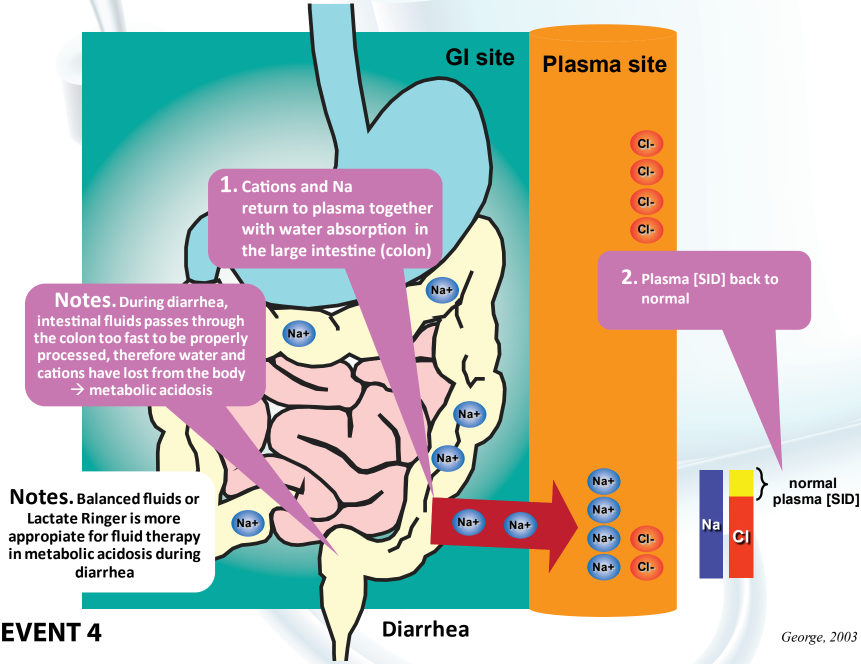
EVENT 1

George, 2003



EVENT 2 & 3

George, 2003

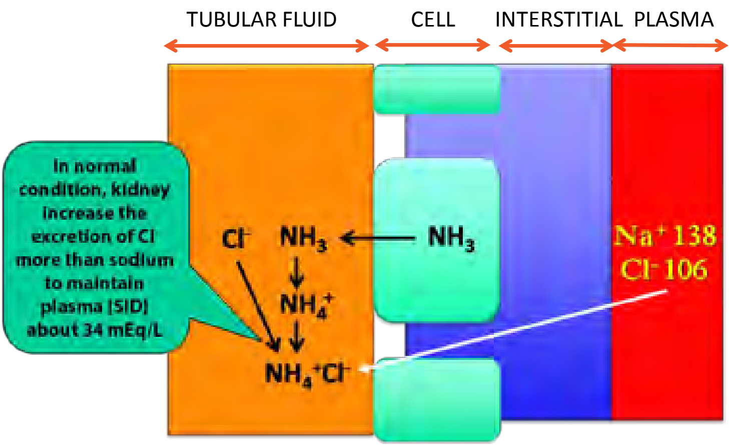


GI site
Plasma site
1. Cations and Na return to plasma together with water absorption in the large intestine (colon)
Notes. During diarrhea, intestinal fluids passes through the colon too fast to be properly processed, therefore water and cations have lost from the body → metabolic acidosis
2. Plasma [SID] back to normal
Notes. Balanced fluids or Lactate Ringer is more appropiate for fluid therapy in metabolic acidosis during diarrhea
Na+
Cl-
Na
Cl
normal plasma [SID]
Diarrhea
EVENT 4
George, 2003

EVENT 4

STRONG ION DIFFERENCE IN KIDNEY

THE KIDNEYS ARE THE MOST IMPORTANT REGULATOR OF [SID] FOR ACID-BASE PURPOSE



George, 2015

EFFECT OF DIURETICS IN URINE COMPOSITION

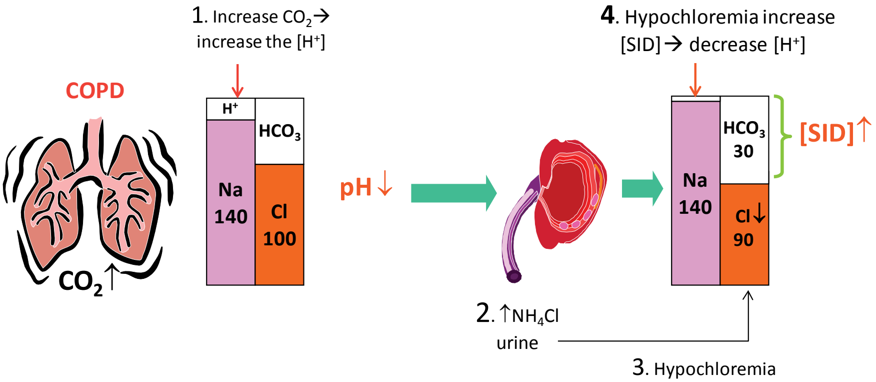
	Volume (ml/min)	pH	Sodium (mEq/l)	Potassium (mEq/l)	Chloride (mEq/l)	SID (mEq/l)
No drug	1	6.4	50	15	60	1
Thiazide diuretics	13	7.4	150	25	150	25
Loop diuretics	8	6.0	140	25	155	1
Osmotic diuretics	10	6.5	90	15	110	4
Potassium-sparing diurtics	3	7.2	130	10	120	15
Carbonic anhydrase inhibitors	3	8.2	70	60	15	120

Loop Diuretics (Furosemide) increase the excretion of Cl^- via urine → reducing urine [SID] and increasing the plasma [SID] → alkalosis

Tonnesen AS, Clincal pharmacology and use of diuretics. In: Hershey SG, Bamforth BJ, Zauder H, eds. Review courses in anesthesiology. Philadelphia: Lippincott, 1983; 217-226

COMPENSATION

Renal Compensation for Chronic Respiratory Acidosis



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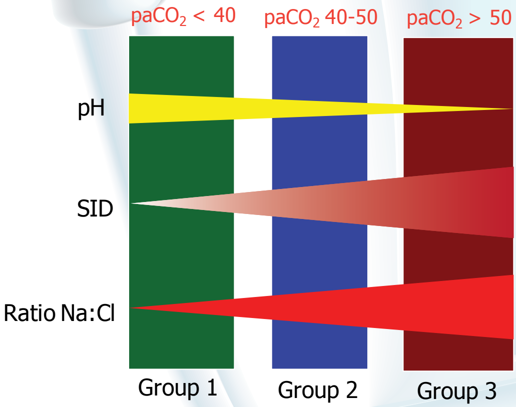
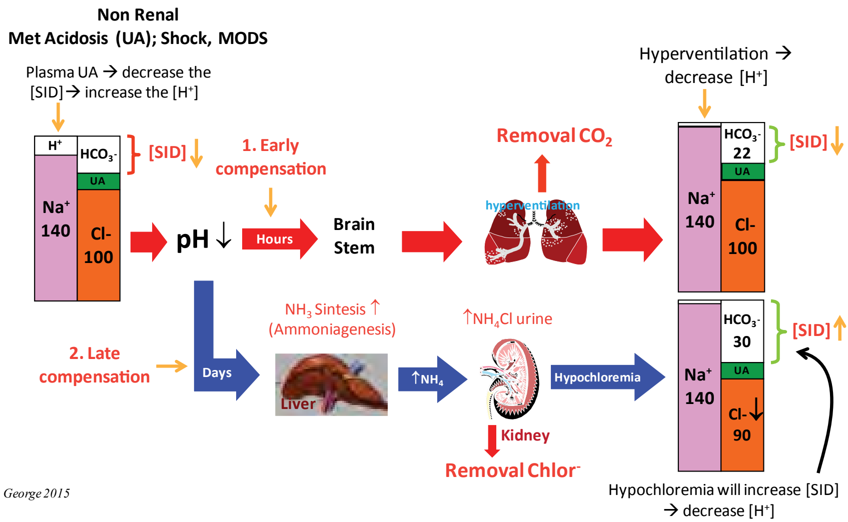
RENAL COMPENSATION FOR CHRONIC RESPIRATORY ACIDOSIS



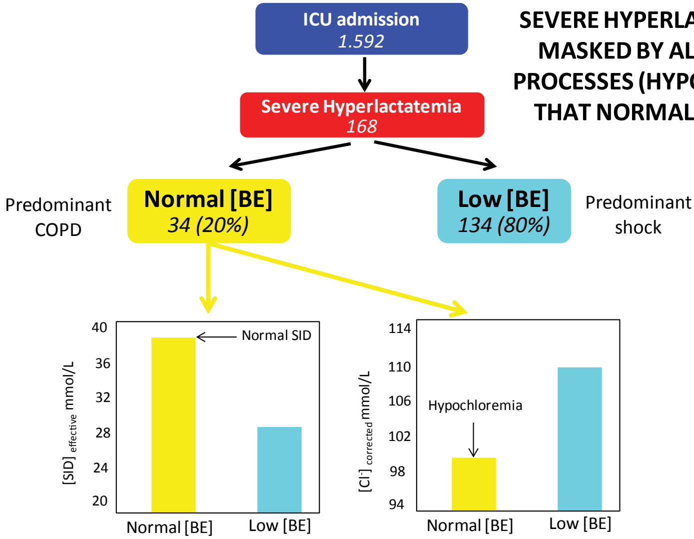
- In stable COPD patients, the plasma pH is preserved closer to normal values in blood through a secondary metabolic compensation by increasing the [SID]. [SID] changes is mainly caused by decreasing plasma Cl^- or hypochloremia

Alfaro T,Torras R, Ibanez J, Palacios L., A physical-chemical analysis of the acid-base response to chronic obstructive pulmonary disease. Can J Physiol Pharmacol 1996 Nov;74(11):1229-35

RENAL & RESPIRATORY COMPENSATION FOR NON RENAL METABOLIC ACIDOSIS (UA) IN STEWART'S TERM



SEVERE HYPERLACTATEMIA IS MASKED BY ALKALINIZING PROCESSES (HYPOCHLOREMIA) THAT NORMALIZE THE [BE]



Tuhay G. Severe hyperlactatemia with normal base excess: a quantitative analysis using conventional and Stewart approaches. Critical Care 2008.

CONCLUSION

- $[H^+]$ in the plasma is determined by [SID], PCO_2 and [Atot] in the plasma
- The strong ion composition of the diet, the function of the GI tract and the function of other tissues may alter plasma [SID] from its normal value
- Plasma [SID] changes by plasma interaction with interstitial fluid through tissue capillary membranes. Interstitial fluid in turn may interact with intracellular fluid through cell membranes.
- Respiration in the lungs and general body circulation regulate alveolar and circulating plasma PCO_2
- The kidney regulate circulating plasma [SID] by differential reabsorption of Na^+ and Cl^-
- When circulating plasma $[H^+]$ changes due to PCO_2 changes, the kidneys slowly produce compensating [SID] changes
- When circulating plasma $[H^+]$ changes due to [SID] changes, respiration in the lungs changes so as to produce compensating plasma PCO_2 changes

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