Understanding Strong Ion Difference

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Physicochemical Approach

Everything you always wanted to know about strong ion difference but were afraid to ask because of the calculations
Acid-base

Strong Ion Difference

- Acid buffering – why and where
- Define cations, anions, strong ions
- Determinants of Acid/Base Status
  Weak ion buffer base, Strong ion difference
- Base Excess
- Anion Gap
- Strong Ion Gap
- Treatment Guidelines
Abnormal Acid/Base Balance

- Predicts outcome
- Often not a direct cause the fatality
  Epiphenomenon
- Acid base homeostasis is defended like
  \( \text{O}_2 \) transport
  Perfusion pressure
Acid/Base Balance

- $[\text{H}^+]$ maintained within nmol/l range
  - Other electrolytes mmol/l range
  - 99.99% $[\text{H}^+]$ is buffered
    - The 0.01% not buffered determines the pH

- $[\text{H}^+]$ effects
  - H-bonds
  - Protein configuration
  - Receptor binding
  - Enzyme activity
    - Rate of glycolysis varies inversely with $[\text{H}^+]$

- Water is an endless supply of $\text{H}^+$
Acid Buffering

- **Plasma**: Immediate buffering
- **Interstitial Fluid**: 15 min
- **Bone (40%)**: 2 – 4 hours
- **Intracellular**: 2 – 4 hours

- **RBC**
Acid/Base Balance

- **Intracellular pH primary importance**
  - pH varies between different cell types
  - pH varies within cellular compartments

- **ECF pH is important physiologically**
  - Conduit for $\text{O}_2$/nutrients to cell
  - It is the fluid that is sensed
    - It is the acid-base regulated by the body
  - pH varies transcellular fluid and interstitial fluid

- **Plasma pH/electrolytes measured**

- **Plasma pH/electrolytes predict intracellular levels**
  - Directly related
# Acid Base measurements

## Arterial vs. Venous sample

<table>
<thead>
<tr>
<th>Source</th>
<th>Venous blood</th>
<th>Arterial blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.162</td>
<td>7.347</td>
</tr>
<tr>
<td>$P_{CO2}$</td>
<td>59.8</td>
<td>28.5</td>
</tr>
<tr>
<td>$P_{O2}$</td>
<td>28.4</td>
<td>92.8</td>
</tr>
<tr>
<td>BE-B</td>
<td>-7.3</td>
<td>-7.8</td>
</tr>
<tr>
<td>$HCO_3$</td>
<td>21.5</td>
<td>15.7</td>
</tr>
<tr>
<td>TCO$_2$</td>
<td>23.4</td>
<td>16.6</td>
</tr>
<tr>
<td>Dextrose</td>
<td>18</td>
<td>50</td>
</tr>
</tbody>
</table>
Physicochemical Approach

- Conservation of mass
  But can have metabolism – e.g. lactate

- Electroneutrality
  Charges always balance

- To balance charge
  $H^+$ produced or donated from weak acid – changes pH
Cations and Anions

• Cations
  \( \text{Na}^+ , \text{K}^+ , \text{Ca}^{++} , \text{Mg}^{++} , \text{H}^+ \)

• Anions
  \( \text{Cl}^- , \text{Lac}^- \)
  \( \text{Hgb, Alb, P}_i \)
  \( \text{Ketones, SO}_4^{2-} \)
  \( \text{Fatty acids, aspirate, glutamate} \)
  \( \text{HCO}_3^- \)
Strong Ions

- Any ion which cannot combine with other ions
  - It is always free
  - Disassociated at physiologic pH
  - Always contributes a charge
- Na\(^+\), K\(^+\), Cl\(^-\)
- Not HCO\(_3\)\(^-\)
  - Weak ion
  - \(\text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O}\)
  - Loses its charge
- Lactate is a strong ion
  - Completely disassociated at physiologic pH
Determinants of Acid/Base Status

- $\text{CO}_2 (\text{Pco}_2)$
- Nonvolatile weak ion acid buffer ($A_{\text{TOT}}$)
- Strong Ion Difference (SID)
CO\(_2\)

- Quantitated as Pco\(_2\)
- CO\(_2\) is in equilibrium with HCO\(_3^-\)
  
  Can calculate HCO\(_3^-\)

  Which is related to SID
Weak Ion Acid Buffer
(Buffer Base)

• Buffer takes up or releases H⁺ in physiologic range of pH changes
• Weak acid buffer
  Volatile
  Nonvolatile
• Volatile buffer HCO₃⁻
  Weak ion - can take a H⁺
  Cannot buffer CO₂ (itself)
    • Not prevent acid-base changes caused by CO₂
    • HCO₃⁻ is not independent
Nonvolatile Weak Ion Acid Buffer

- $A_{Total} = A^- + AH$
  - Hemoglobin
  - Albumin
  - Inorganic phosphates
- $A^-$ changes with SID & Pco$_2$ – dependent
- $A_{Total}$ not change – independent
- Good buffers
  - Even at extremes of concentrations
- There's no single dissociation constant
  - Large number of buffering sites
  - Most effective near normal pH
Nonvolatile Weak Acid Buffer

- \( AH = \)
  - In plasma – Albumin + \( P_i^- + SO_4^{2-} \)
  - In RBC – Hb + \( P^- \)
- **Estimate \( A^- \)**
  - Using only total protein
  - Using albumin & \( PO_4^{2-} \)
    - \( A^- = 2 \text{ (albumin)} + 0.5 \text{ (Pi)} \)
    - \( pH < 7.35 \)
    - \( A^- = pH \left[(1.16 \times \text{albumin}) + (0.42 \times \text{Pi})\right] – (5.83 \times \text{albumin}) – (1.28 \times \text{Pi}) \)
Cations/Anions

Weak Ion Acid Buffer

Cations

Na\(^+\)

Anions

A\(^-\)

HCO\(_3\)^-

Cl\(^-\)

P\(_i\)^-  SO\(_4\)^{2-}  Alb^-  Hb^-
Acid/Base Balance

• As independent factors change
  \( \text{CO}_2, \text{SID, A}_{\text{Total}} \)
• “+” = “-”
  Charges must remain balanced
• Dependent factors adjust
  To keep charge balanced and maintain pH
  \( A^- + H^+ \rightleftharpoons AH \)
  \( H^+ + \text{HCO}_3^- \rightleftharpoons \text{CO}_2 + \text{H}_2\text{O} \)
SID (Strong Ion Difference)

- Old concept - new name
  
  Change from normal = BE

- Strong ions
  
  Lactate, Hydroxybutyrate, SO$_4^{2-}$, Na$^+$, K$^+$, Cl$^-$

  $\text{SID} = (\text{Na}^+ + \text{K}^+ + \text{Ca}^{++} + \text{Mg}^{++}) - \text{Cl}^-$

  $\text{SID} = \text{HCO}_3^- + \text{A}^-$

  $\text{SID} = 40-42$ (ICU patients = 30)
Cations/Anions

SID

Cations

Na⁺
Mg⁺⁺
Ca⁺⁺
K⁺

Anions

Cl⁻
SID
Base Excess

• Definition
  
  Blood gas measured pH and $P_{co2}$

  If adjust $P_{co2} = 40$
  
  • pH will change

  If adjusted pH $\neq 7.40$
  
  • Amount of added base needed to pH = 7.40

• It eliminates the respiratory component

• It defines the metabolic derangement
  
  Causing the abnormal pH
Base Excess

- Base excess =
  Change in $A^- + HCO_3^-$ from normal
  Change in SID from normal
- $+\ BE =$ metabolic alkalosis
- $-\ BE =$ metabolic acidosis
- $BE =$ SIDex
- $BE$ from ABG machine
  Calculation assumes
  - $A_{TOT} =$ blood with Hb of 5 g/dl and $P_{CO_2} = 40$
Hyperchloremic Acidosis

Cations

\[ \uparrow \text{Na}^+ \]

\[ \uparrow \text{SID} \]

\[ \downarrow \text{H}^+ \]

Anions

\[ \downarrow \text{SID} \]

\[ \downarrow \text{Cl}^- \]

\[ \downarrow \text{CO}_2 \text{HCO}_3^- \]

\[ \downarrow \text{AH} \]
Lactic Acidosis

Cations

Na⁺

Anions

Cl⁻

SID

HCO₃⁻

BE

Lac⁻

AH⁻

CO₂⁻

↑H⁺
Anion Gap

- \( \text{Na}^+ + \text{K}^+ = \text{Cl}^- + \text{HCO}_3^- + A^- \)
- \( \text{AG} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-) \)
  \[ \text{AG} = A^- = \text{ionized albumin} + P_i^- \]
- Normal AG range is large
  - Because albumin + \( P_i \) range large
  - Hypoproteinemia - normal AG with lactic acidosis
- Usually measured in venous blood
  - With \( T_{co_2} \) used to estimated \( \text{HCO}_3^- \)
Cations/Anions

Anion Gap

Cations

K⁺

Na⁺

Anions

HCO₃⁻

Cl⁻

AG

A⁻

Lac⁻
Anion Gap Acidosis Artifacts

- Dehydration
  Concentrating all ions
- Na salts
  High doses Na penicillin (beta lactams)
  Na lactate
  Na acetate
- Decreased unmeasured cations
  ↓Mg
  ↓Ca
- Hypoalbuminemia
  Severe
  ↓AG by 2.5-3 mEq/l for each 1 g/dl decrease
Anion Gap Acidosis
Artifacts

- Respiratory and metabolic alkalosis
  $\uparrow$3-10 mEq/liter in apparent AG
- Parenteral nutrition
  Formulas with acetate
- Multiple blood transfusions
  Increased citrate
  Large volumes
- Unidentified cations
Corrected Anion Gap

- ICU patient
  - Albumin and $P_i$ not normal
  - Unmeasured anions which make normal gap
- As long as pH < 7.35
  - "Normal" AG
    - $= 2 \text{ (albumin g/dl)} + 0.5 \text{ (P}_i\text{ mg/dl)}$
    - $\pm 5$ at best
Strong Ion Difference vs. Anion Gap

- **Strong Ion Difference**
  
  \[
  \text{SID} = (\text{Na}^+ + \text{K}^+ + \text{Ca}^{++} + \text{Mg}^{++}) - (\text{Cl}^- + \text{Lac}^-)
  \]

- **Anion Gap**
  
  \[
  \text{AG} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)
  \]
**Strong Ion Gap (SIG)**

- **SID effective**
  
  \[ \text{SID effective} = A^- + HCO_3^- = \text{SIDe} \]

- **SID apparent**

  \[ \text{SID apparent} = (\text{Na}^+ + \text{K}^+ + \text{Ca}^{++} + \text{Mg}^{++}) - (\text{Cl}^- + \text{Lac}^-) = \text{SIDa} = 40-42 \text{ (healthy human)} \]

- **SIDe = SIDa**

  If not there are unmeasured ions

  Difference is SIG
Metabolic Acidosis
Increase in Unidentified Anions
SIG < 0
Metabolic Alkalosis
Unidentified Cation Alkalosis
SIG > 0
Strong Ion Gap (SIG)

- SIG = SIDe – SIDa
- SIG < 0 – unmeasured anions
  - Sepsis
  - Liver disease
    - liver clears unmeasured anions
    - with sepsis, failure → liver releases anions

If lactate is not part of SIDa
- Most common cause of SIG > 0
- Lactate mmol/l = SIG

- SIG does not change with
  pH changes
  Changes in albumin
Treatment Guidelines

- Normalize pH
- If SIG ≠ 0
  - Investigate unmeasured ions
    - Treat underlying cause
- If SIG = 0, with acidosis
  - ↓ SID
    - ↑ SID – give fluids Na > Cl
      - NaHCO₃
  - ↑ SID
    - Compensation already occurring
Treatment Guidelines

• If SIG = 0, with alkalosis
  ↑ SID
  • ↓ SID – give fluids low SID (NaCl)
  • Will expand ECF
  ↓ SID
  • Compensation already occurring

• Lactate special case
  Don’t treat with NaHCO3
  • Lactate clears rapidly
  • Overshoot alkalosis and Na overload
  Severe acidosis interferes with Lactate metabolism
  • pH < 7.20
  Treat cause of ↑ lactate
Case 1
Lactic Acidosis

- NI foal
- Present 12 hrs old
  - PCV 5%
  - TP 6.1
  - Glu <10
  - Temp 97.7
  - HR 140
  - RR 35
Case 1
Lactic Acidosis

- Lactate out of range
- SIG = -20.8
  Lactate not in SIDa
  Unidentified anion = lactate
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A strong ion is any ion which cannot combine with other ions so it is always free (disassociated). Na⁺, K⁺, Cl⁻ are strong ions but HCO₃⁻ is a weak ion since it can combine forming H₂CO₃, CO₂, H₂O and lose its charge. The strong ion indifference (SID) is the net charge difference between strong ions. The SID dictates the net charge of weak ions so that SID = HCO₃⁻ + A⁻.

Three independent determinants of acid-base status: [H⁺]

1. CO₂ (Pco₂): Since CO₂ is in equilibrium with HCO₃⁻ if Pco₂ is known, can calculate HCO₃⁻ which is in turn = SID.
2. Nonvolatile weak acid buffer: Hemoglobin, albumin, inorganic phosphates (A₋₉ₒ). A⁻ = (Na⁺ + K⁺ + Ca⁺⁺ + Mg⁺⁺) – (Cl⁻ + Lac⁻)
3. SID: SID = HCO₃⁻ + A⁻ = (Na⁺ + K⁺ + Ca⁺⁺ + Mg⁺⁺) – (Cl⁻ + Lac⁻)

Kidney regulation of acid-base status can be thought of in terms of H⁺ and HCO₃⁻ or SID, which are mirror images of each other. Treatment with NaHCO₃ will result in excretion of HCO₃⁻ and retention of Cl⁻ relative to Na and K resulting in decreased SID. Increased urine SID will force HCO₃⁻ excretion to preserve electrical neutrality of the urine.

Gastrointestinal shifts in acid and base can also be thought of in terms of strong ions rather than H⁺ and HCO₃⁻. In the stomach, parietal cells secrete Cl⁻ which is a strong cation forcing H⁺ secretion. Since gastric mucosa and mucus layer can support a large pH gradient (lumen to cells), the lumen maintains high a H⁺ concentration. When gastric fluid moves to the small intestine the Cl⁻ is neutralized by secreted NaHCO₃ and NaCl is resorbed together. In the colon, reabsorbed of K⁺ and Na⁺, which was secreted higher in the tract will maintain the SID. With diarrhea K⁺ and Na⁺, which are trapped in the lumen, are lost decreasing SID which can result in a hyperchloremic acidosis.

Anion Gap

The anion gap is another way of looking at the mix of strong and weak ions. Traditionally it has been used to detect lactic acidosis, ketoacidosis and the presence of certain poisons. Anion gap is usually measured in venous blood with HCO₃ estimated as total CO₂. The derivation of the anion gap comes from the relationship of conservation of charges of anions and cations:

Na⁺ + K⁺ = Cl⁻ + HCO₃⁻ + A⁻

AG = Na⁺ + K⁺ - Cl⁻ - HCO₃⁻

So the anion gap really is A⁻ which usually consists of ionized albumin and Pₗ (inorganic phosphates). Plasma proteins other than albumin have mixed charges that in aggregate are neutral. The normal anion gap is between 3 and 11 mM in plasma. The normal range is large because
Normal albumin and inorganic phosphors levels can vary a large amount. This causes a problem in interpreting AG in the face of hypoproteinemia which is a common finding in neonates. With hypoproteinemia the patient may have a normal AG in the face of lactic acidosis. Because of its dependence on albumin and phosphorus levels, the normal anion gap for a patient can be estimated if the albumin and phosphorus levels are known using the following formulas (as long as pH < 7.35):

\[
\text{Normal AG} = 2 \times \text{albumin} + 0.5 \times \text{P}_i
\]

\[
\text{AG} = \text{A}^- - \text{pH} \times \left[0.16 \times \text{albumin} + 0.42 \times \text{P}_i\right] - 5.83 \times \text{albumin} - 1.28 \times \text{P}_i
\]

Deviations from what is calculated using albumin and phosphorus represents the presence of unmeasured anions which are contributing to the acid-base imbalance. Unmeasured anions occur in sepsis and liver disease and experimentally in endotoxemia.

Although an increase in AG is usually interpreted to suggest the presence of sepsis, ketosis, lactic acidosis, poisoning or renal failure there can be artifacts caused by a number of factors. Dehydration will cause a false increase in AG by concentrating all ions. Severe hypoalbuminemia will cause a decrease in AG by 2.5-3 mEq/liter for each 1 g/dl decrease. Respiratory and metabolic alkalosis will cause an increase by 3-10 mEq/liter in apparent AG because of increased lactate production from increased phosphofructokinase activity, decreased A^- and dehydration effect. Administration of large amounts of Na or K salts of beta lactams will also increase apparent AG. Parenteral nutrition formulas with acetate will increase apparent AG. Large volume blood transfusions (increased citrate transfused) will increase apparent AG. Most of these situations can be readily identified and will not change AG much.

**Strong Ion Gap (SIG)**

Another way to predict the presence of unmeasured strong ions which may be affecting pH is to calculate the strong ion gap (SIG). This is the gap between the apparent SID [\(\text{SIDa} = (\text{Na}^+ + \text{K}^+ + \text{Ca}^{++} + \text{Mg}^{++}) - (\text{Cl}^- + \text{Lac}^-)\)] and the effective SID [\(\text{SIDe} = \text{A}^- + \text{Tco}_2\)]. If \(\text{SIDe} \neq \text{SIDa}\) there are unmeasured strong ions or a SIG. If \(\text{SIDa} > \text{SIDe}\) there are unmeasured anions present as occurs in sepsis or liver disease. Usually the liver clears unmeasured anions but with sepsis the liver releases such anions. If \(\text{SIDa} < \text{SIDe}\) there are unmeasured cations. Unlike AG, SIG does not change with pH or changes in albumin and normally \(\text{SIG} = 0\) thus eliminating the variability of the AG normal range.