Understanding Strong Ion Difference

Jon Palmer, VMD, DACVIM
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
- Metabolic acid-base control
- Metabolic acidosis
- Metabolic alkalosis
Abnormal Acid/Base Balance

- Predicts outcome
- Often not a direct cause the fatality
  Epiphenomenon
- Acid base homeostasis is defended like
  \( O_2 \) transport
  Perfusion pressure
Acid/Base Balance

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

- \([H^+]\) effects
  - H-bonds
  - Protein configuration
  - Receptor binding
  - Enzyme activity
    - Rate of glycolysis varies inversely with \([H^+]\)

- Water is an endless supply of H^+
Acid –Base balance

- **CO2 is an acid**
  - Excreted from cell - liberates H+ from H₂O
  - It returns H⁺ to water when it is exhaled
  - CO₂ + H₂O → H₂CO₃ → H⁺ + HCO₃⁻

- [H⁺] in tissues is very small
  - 1/1,000,000 of HCO₃⁻

- Neutral pH at 37°C = 6.8
  - At 0°C pH = 8.0
  - Arterial plasma pH 0.6 > neutral (pH = 7.4)
    - All species regardless of normal temperature
    - pH inside cell it is closer to neutral pH
Acid Buffering

- Plasma
  - Immediate buffering

- Interstitial Fluid
  - 15 min

- Bone
  - (40%)

- 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 $O_2$/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>$P_{CO_2}$</td>
<td>59.8</td>
<td>28.5</td>
</tr>
<tr>
<td>$P_{O_2}$</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>

**Note:** The values for the BE-B column are negative, indicating a metabolic acidosis in the venous sample and a metabolic alkalosis in the arterial sample.
Physicochemical Approach

- Conservation of mass
  But can have metabolism – e.g. lactate
- Electroneutrality
  Charges always balance
- To balance charge
  $\text{H}^+$ produced or donated from weak acid – changes pH
Cations and Anions

- **Cations**
  - Na$^+$, K$^+$, Ca$^{++}$, Mg$^{++}$, H$^+$

- **Anions**
  - Cl$^-$, Lac$^-$
  - Hgb, Alb, P$_i$
  - Ketones, SO$_4^{2-}$
  - Fatty acids, aspirate, glutamate
  - HCO$_3^-$
Cations/Anions

Cations

- H^+
- Mg^{++}
- Ca^{++}
- K^+

Na^+

Anions

- Cl^-
- P_i^-
- SO_4^{2-}
- Hb^-
- Alb^-
- Lac^-

HCO_3^-
Strong Ions

- Any ion which cannot combine with other ions
  - It is always free
  - Disassociated at physiologic pH
  - Always contributes a charge
- \(\text{Na}^+, \text{K}^+, \text{Cl}^-\)
- Not \(\text{HCO}_3^-\)
  - 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

- CO$_2$ (Pco$_2$)
- Nonvolatile weak ion acid buffer ($A_{TOT}$)
- Strong Ion Difference (SID)
CO₂

• Quantitated as Pco₂

• CO₂ is in equilibrium with HCO₃⁻

  Can calculate HCO₃⁻

  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 $HCO_3^-$
  - Weak ion - can take a $H^+$
  - Cannot buffer $CO_2$ (itself)
    - Not prevent acid-base changes caused by $CO_2$
    - $HCO_3^-$ 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\textsubscript{i} - + SO\textsubscript{4}^{2-}
  - In RBC – Hb + P -

- **Estimate A\textsuperscript{-}**
  - Using only total protein
  - Using albumin & PO\textsubscript{4}^{2-}
    - A\textsuperscript{-} = 2 (albumin) + 0.5 (Pi)
    - pH < 7.35
    - A\textsuperscript{-} = pH [(1.16 X albumin) + (0.42 X Pi)] – (5.83 X albumin) – (1.28 X Pi)
Cations/Anions
Weak Ion Acid Buffer

Cations

Na⁺

Anions

A⁻

HCO₃⁻

Cl⁻
Pᵢ⁻  SO₄²⁻
Alb⁻  Hb⁻
Acid/Base Balance

• As independent factors change
  \( CO_2, \text{ SID}, A_{\text{Total}} \)
  \[ “+” = “-” \]
  Charges must remain balanced

• Dependent factors adjust
  To keep charge balanced and maintain pH
  \[ A^- + H^+ \leftrightarrow AH \]
  \[ H^+ + HCO_3^- \leftrightarrow CO_2 + H_2O \]
SID (Strong Ion Difference)

- Old concept - new name
  Is Buffer Base
  Change from normal = BE (Standard BE)

- Strong ions
  Lactate, Hydroxybutyrate, $SO_4^{2-}$, Na$^+$, K$^+$, Cl$^-$
  \[
  SID = (Na^+ + K^+ + Ca^{++} + Mg^{++}) - Cl^- \\
  SID = HCO_3^- + A^- \\
  SID = 40-42 \text{ (ICU patients = 30)}
  \]
Milligram-Milliequivalent Conversions

\[ m\text{Eq/L} = \frac{(mg/L) \times \text{valence}}{\text{formula wt}} \]

\[ mg/L = \frac{(m\text{Eq/L}) \times \text{formula wt}}{\text{valence}} \]

**ATOMIC WEIGHTS OF SOME COMMON ELEMENTS***

<table>
<thead>
<tr>
<th>Element</th>
<th>Atomic Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen (H)</td>
<td>1</td>
</tr>
<tr>
<td>Magnesium (Mg)</td>
<td>24</td>
</tr>
<tr>
<td>Carbon (C)</td>
<td>12</td>
</tr>
<tr>
<td>Phosphorus (P)</td>
<td>31</td>
</tr>
<tr>
<td>Nitrogen (N)</td>
<td>14</td>
</tr>
<tr>
<td>Chlorine (Cl)</td>
<td>35.5</td>
</tr>
<tr>
<td>Oxygen (O)</td>
<td>16</td>
</tr>
<tr>
<td>Potassium (K)</td>
<td>39</td>
</tr>
<tr>
<td>Sodium (Na)</td>
<td>23</td>
</tr>
<tr>
<td>Calcium (Ca)</td>
<td>40</td>
</tr>
</tbody>
</table>

*Atomic weights are approximate.
Milligram-Milliequivalent Conversions

- \( \text{Ca mEq/l} = \frac{\text{mg/dl} \times 10 \times 2}{40} \)
- \( \text{Ca mEq/l} = \text{Ca mg/dl} \times 0.5 \)
- \( \text{Mg mEq/l} = \frac{\text{mg/dl} \times 10 \times 2}{24} \)
- \( \text{Mg mEq/l} = \text{Mg mg/dl} \times 0.83 \)
Cations/Anions

SID

Cations

Mg$^{++}$
Ca$^{++}$
K$^{+}$

Na$^{+}$

Anions

SID

Cl$^{-}$
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
- $+ BE = \text{metabolic alkalosis}$
- $- BE = \text{metabolic acidosis}$
- $BE = \text{SIDex}$
- $BE \text{ from ABG machine}$
  - Calculation assumes
    - $A_{TOT} = \text{blood with Hb of 5 g/dl and } P_{CO2} = 40$
Base Excess

- **Plasma alone**

- **RBC alone**
  - Much different from plasma
  - Estimated from plasma
    - Using Gibbs- Donnan equation - only measure plasma value

- **RBC + plasma = BE-B**

- **ECF – including plasma**
  - Estimated from plasma
    - Using Gibbs- Donnan equation - only measure plasma value

- **RBC + ECF = BE-ECF; SBE**
Standard Base Excess

- Metabolic abnormalities of the ECF
  ECF = plasma + RBC + interstitial fluid
  BE of whole blood + interstitial fluid
  ECF is the conduit for O_2/nutrients to cell
  It is the fluid that is sensed
  - It is the acid-base regulated by the body

- SBE = 0.9287 (HCO_3^- - 24.2 + 14.83 (pH - 7.4))
  SIDexcess of ECF
  Calculation assumes
  - A_TOT of ECF = blood with Hb of 5 g/dl and Pco2 = 40
Hyperchloremic Acidosis

Cations

Na⁺

↑H⁺

SID

BE

Anions

Cl⁻

AH

A⁻

HCO₃⁻

CO₂
BE
Lactic Acidosis

Cations

Na⁺

↑H⁺

Anions

Cl⁻

SID

Lactate H⁺

BE

SID

HCO₃⁻

Lac⁻

Na⁺

↑H⁺
Standard Base Excess

- If hemoglobin = 1 g/dl – error only 3 mM
- If $\text{Pco}_2 = 100$ – error only 3 mM
- Patients with varying protein buffer conc
  Respond similarly to abnormalities of acid-base
- $\text{SBE} = \text{SID change required to produce}$
  $\text{pH} = 7.4$ at $\text{Paco}_2 = 40$ with the prevailing $A_{\text{TOT}}$
  Amount $\uparrow P_{\text{Na}}$ (with Na bicarbonate) to correct
Cations/Anions
SID

Cations

Mg$^{++}$
Ca$^{++}$
K$^{+}$

Na$^{+}$

Anions

SID

A$^{-}$
HCO$_3^{-}$
Cl$^{-}$
Anion Gap

• \( \text{Na}^+ + \text{K}^+ = \text{Cl}^- + \text{HCO}_3^- + \text{A}^- \)

• \( \text{AG} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-) \)
  \( \text{AG} = \text{A}^- = \text{ionized albumin} + \text{P}_i^- \)

• **Normal AG range is large**
  
  Because albumin + \( \text{P}_i \) range large
  
  Hypoproteinemia - normal AG with lactic acidosis

• **Usually measured in venous blood**
  
  With \( \text{Tco}_2 \) used to estimated \( \text{HCO}_3^- \)
Cations/Anions
Anion Gap

Cations

| H+ | Na+ | K+ |

Anions

| AG | A- | A- | HCO3- | HCO3- | Cl- | Cl- | Lac- | AG |
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
  \( \uparrow 3-10 \text{ mEq/liter in apparent AG} \)

- 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
    - $\text{AG} = A^- = pH \left[ (1.16 \times \text{albumin} ) + (0.42 \times P_i) \right] - (5.83 \times \text{albumin}) - (1.28 \times P_i)$
Strong Ion Difference vs. Anion Gap

• Strong Ion Difference

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

• Anion Gap

\[ \text{AG} = (Na^+ + K^+) - (Cl^- + HCO_3^-) \]
Strong Ion Gap (SIG)

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

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

- 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)

- \( \text{SIG} = \text{SID}_e - \text{SID}_a \)
- \( \text{SIG} < 0 \) – unmeasured anions
  - Sepsis
  - Liver disease
    - Liver clears unmeasured anions
    - With sepsis, failure \( \rightarrow \) liver releases anions
  - If lactate is not part of \( \text{SID}_a \)
    - Most common cause of \( \text{SIG} > 0 \)
    - Lactate mmol/l = SIG
- \( \text{SIG} > 0 \) – increased unidentified cations
- SIG does not change with
  - pH changes
  - Changes in albumin
Metabolic Acidosis

- Metabolic acidosis
  - ↓ SID → Results in ↑ free H+ → acidosis
- ↓ SID
  - ↑ Organic acids – ↑ Lactate, ↑ Ketones
  - Loss of cations – diarrhea
  - Mishandling of ions -- renal tubular acidosis
  - Addition of exogenous ions -- iatrogenic, poisoning
- Treat metabolic acidosis
  - ↑ Na⁺ > ↑ Cl⁻ e.g. NaHCO₃
**Metabolic Alkalosis**

- **Metabolic alkalosis**
  - ↑SID → Results in ↓ free H+ → alkalosis
- **↑SID**
  - Loss of anions > cations
  - Diuretics
  - Renal disease
- **Treatment**
  - cations > anions
  - Replacing Cl⁻ e.g. NaCl, KCl, HCl
  - Cl resistant alkalosis
    - Only because of ongoing renal loss of Cl⁻ - RTA
    - Hyperaldosteronism
Pathophysiology
Disorders of acid-base balance

- Acid-base abnormalities
  Only occur with failure to compensate
  - Disorders primary regulating organs
  - Exogenous drugs/fluids
    Alter ability to maintain acid-base balance
  - Abnormal metabolism
    Overwhelms ability of defense mechanisms

- SID is regulated by the kidneys/GI tract
Acid-Base Balance
Renal Regulation

- Renal excretion strong ions
  Most reabsorbed automatically
  Only able to excrete small amounts per min
  Thus it takes hours for a renal response
- Diet – similar ratios of strong cations/anions
  Sufficient Cl available to filter
  If not reabsorbed – ↑SID
- Cl excretion – primary regulating mechanism
  Na/K handling – other priorities – not acid-base
Pathophysiology
The Kidney - Urine pH

• Independent of plasma pH
• Independent of renal "acid" excretion
• \( \text{pH} = \text{amt H}^+ \)
  Not amt \( \text{NH}_4^+ \)
  Not amt other “fixed acids”
Can have high rate acid excretion
  • But alkaline urine pH
Pathophysiology
Ammoniagenesis

• Excrete Cl\(^-\) without Na\(^+\) or K\(^+\) - regulate SID
  
  As Cl\(^-\)NH\(_4^+\)

• Renal-Hepatic Interaction
  
  NH\(_4^+\) – co-excretion with Cl\(^-\)
  
  • Not because the H\(^+\)

  NH\(_4^+\) produced in the kidney and liver
Pathophysiology
Ammoniagenesis

• Hepatic glutaminogenesis
  Stimulated by acidosis

• Nitrogen metabolism in liver
  → Urea, glutamine, (NH$_4^+$)
  Glutamine → kidney → ↑NH$_4^+$ → ↑Cl$^{-}$ excretion
  ↑Glutamine → alkalosis by ↓Cl$^{-}$ relative to Na$^+$
Hepatocyte with urea production capacity

Closer to portal vein

GI tract $\text{NH}_4^+$ $\rightarrow$ urea first

Acidosis inhibits urea formation

- $\text{NH}_4^+$ to glutamine producing cells $\rightarrow$
  - $\uparrow$Glutamine production $\rightarrow$

- Kidney $\rightarrow$ $\text{NH}_4^+$ $\rightarrow$ $\uparrow$Cl$^-$ loss $\rightarrow$ compensatory Alk
Pathophysiology
Gastrointestinal tract

- Important cause of acid-base imbalance
- *Stomach* – Cl⁻ pumped out of plasma →
  ↓SID in gastric juices → acid
  ↑SID in plasma → "Alkaline tide" with meal
- *Duodenum* – Cl⁻ is reabsorbed →
  Return SID of plasma
- Reflux → loss of Cl⁻ → alkalosis (↑SID)
- *Pancreas* -- fluid has ↑SID (↓Cl⁻) →
  Plasma ↓SID → peaks after meal (counter act alkaline tide)
  If reflux → plasma remains acidotic (↓SID – ↑Cl⁻)
Pathophysiology
Gastrointestinal tract

• **Colon** -- fluid ↑SID
  Most of Cl⁻ removed in small intestine
  Na⁺/K⁺ left in lumen
  Should absorb Na⁺ and water
    - If diarrhea → lose Na⁺/K⁺ relative to Cl⁻ → acidosis

• **Can GI tract compensated in acidosis/alkalosis??**
  Not been studied
  Endotoxemia may remove anions →
    • ↑SID in plasma → ↑alkalosis
Clinical Effects Of Metabolic Acidosis

• Brief exposure to acidosis well tolerated
  Exercise - pH < 7.15, lactate > 20 mEq/liter

• Chronic mild acidosis (pH < 7.35)
  Metabolic bone disease
  Protein catabolism

• Critically ill patients
  Not tolerate even brief acidosis

• Metabolic acidosis patients
  Poorer outcome than respiratory acidosis
  Cause more important than degree of acidosis
  Epiphenomenon
Potential Clinical Effects of Metabolic Acidosis

- **Cardiovascular**
  - ↓Inotropy
  - Conduction defects
  - Arterial vasodilation
  - Venous vasoconstriction

- **02 Delivery**
  - ↓Oxyhemoglobin binding
  - ↓ 2,3-DPG (late)

- **Electrolytes**
  - ↑K, ↑Ca
  - Hyperuricemia
Potential Clinical Effects of Metabolic Acidosis

- **Neuromuscular**
  - Respiratory depression
  - Decreased sensorium
- **Metabolism**
  - Protein wasting
  - Bone demineralization
  - Insulin resistance
  - Catecholamine stimulation
  - PTH stimulation
  - Aldosterone stimulation
ICU Patients

Cations

Na⁺

SID

Anions

A⁻

Cl⁻

A⁻

SID
Metabolic Acidosis

- ICU patients SID = 30
  - Less reserve
  - ↑Lac or ↑NaCl treatment → more effect
  - Have lower SID without evidence of acidosis
    - Secondary to ↓alb → ↓A-
    - No compensatory ↓Pco2 for other reasons
    - So must ↓SID to maintain the pH

- ↓SID → ↓pH not linear
  - As SID < 20 → greater ↓pH
  - As SID approaches 20 → small insult ↓↓↓pH
Metabolic Acidosis
Strong ion acidosis

- Lactic acidosis
- Hyperchloremic acidosis
Lactic Acidosis

- Cardinal sign of septic shock
  Synonymous with hypoperfusion
  Mistakenly used as a gauge of perfusion
- Common in septic patients
  With good perfusion
Source of Lactate in Sepsis

- **Septic shock**
  - Increase ATP requirement
  - Anaerobic metabolism
  - Rapid increase lactate levels

- **Sepsis without shock**
  - “Stress” lactic acidosis
  - Cytokine mediated
    - IL-1beta, IL-6 and TNF alpha
Normally

Glucose ➔ Glucose

glycolysis

Pyruvate dehydrogenase

Pyruvate ➔ Lactate ➔ Pyruvate

Acetyl-CoA

Kreb’s Cycle

Lactate ➔ Lactate

α-ketoglutarate ➔ Isocitrate • OOA ➔ Citrate
Acetyl-CoA
Citrate
Kreb's Cycle
Pyruvate
glycolysis
Glucose
Lactate
Traditional view
O2
Pyruvate dehydrogenase
α-ketoglutarate
Isocitrate
Glucose
Lactate
Pyruvate
Glucose → glycolysis → Pyruvate → Acetyl-CoA → Kreb’s Cycle

But ...

Pyruvate dehydrogenase

Lactate → Pyruvate
Glucose → glycolysis → Pyruvate → Acetyl-CoA → Kreb’s Cycle

- Lactate
- Pyruvate dehydrogenase
- OOA
- Citrate
- α-ketoglutarate
- Isocitrate

But ...
Lactate Sources

- **Tissue Hypoxia**
  - Hypodynamic shock
  - Organ ischemia

- **Hypermetabolism**
  - Increased aerobic glycolysis
  - Increased protein catabolism
  - Increased muscle activity – shivering

- **Decreased Clearance of Lactate**
  - Shock – poor liver perfusion
  - Cytokine-mediated
  - Liver failure

- **Inhibition of Pyruvate Dehydrogenase**

- **Activation of Inflammatory Cells**
Source of Lactate in Sepsis

- Pyruvate dehydrogenase block
  - Cytokine down-regulation
  - Relative thiamine deficiency
  - Forces glucose → lactate production

- SIRS Hypermetabolism
  - Increase cellular glucose uptake
  - Stress hormone mediated
    - Epinephrine
  - Cytokine-mediated modulation of glucose transporter
    - ↑ synthesis
    - ↑ activity
    - ↑ distribution
  - ↑ glucose entry into cells
    - Mass action → ↑ glycolytic flux → ↑ lactate production
Source of Lactate in Sepsis

- Phagocytes major cellular source
  Required energy for respiratory burst
  Occurs where macrophages are active
    - Damaged organ or site of trauma
    - Liver, spleen, gut, lung, wound

- Decreased hepatic lactate clearance
  Sepsis impairs liver clearance
Lactate Accumulation
Epinephrine Surge

- After injury, in sepsis, at birth
- Stimulates $\text{Na}^+:\text{K}^+$ ATPase
  - $\uparrow\uparrow$ Aerobic glycolysis $\rightarrow\uparrow$ lactate production
  - Coupled to $\text{Na}^+:\text{K}^+$ ATPase activity in muscle
    - At rest, $< 10\%$ of its total $\text{Na}^+:\text{K}^+$ ATPase
      - Maintain Na:K gradients
Lactate Accumulation

Epinephrine Surge

- \( \uparrow \) Activity \( \text{Na}^+:\text{K}^+ \) ATPase
  - \( \uparrow \) Lactate production
    - Under well-oxygenated conditions

One cause of \( \downarrow \text{K} \)

- Inhibition of \( \beta_2 \)-adrenoreceptors
  - Prevents muscle associated lactate increase
  - Confirms mechanism Epinephrine increase lactate

- Epinephrine results in
  - Lactatemia
  - Hypokalemia
Lactate Accumulation
Clearance by Tissues

- Liver
  Large capacity for lactate removal
- Other organs
  Kidneys
  GI tract
  Muscles
- Lactate clearance reduced by
  Sepsis
  Alkalosis
  Acidosis (pH < 7.20)
  Liver failure
Hyperlactatemia without acidemia

- Large quantities of Na lactate administered
  Alkalemia occurs as lactate is metabolized
- Chronic lactate accumulation
  Chloride ions move out of the vascular space
  Compensatory increase SID
- Endogenous hyperlactatemia
  Initially always associated acidosis
  Normal pH or alkalosis
    - Suggests relative chronicity
    - Hypochloremic increase SID
Lactic Acidemia

- Nonspecific marker of hypoperfusion
- Important marker of tissue distress

Malmetabolism
Lactate Levels
Hypoperfusion

- Traditionally
  Increased blood lactate = hypoxia/hypoperfusion
  Tissue hypoxia $\rightarrow$ MODS/death
- Fundamental goal of therapy
  Restoration of cellular oxygen delivery
- Reliable indicators of adequate perfusion
  Warm legs
  Strong peripheral pulses
  Organ function - Urine output, Mental status, Borborygmi
- Lactate levels elevated
  With hypoperfusion
  With normal perfusion
- Decrease lactate levels
  A goal of cardiovascular support
  Not exclusive goal
  Pressor therapy may cause significant increase lactate
Lactate Levels

Hypoperfusion

- Blood lactate
  - Guide to resuscitation
- Epinephrine surge
  - Occurs
    - Normal birth
    - SIRS - Sepsis/septic shock
    - Hypoxic ischemic asphyxial insult
  - Greatly accelerate aerobic glycolysis and lactate production
    - Coupled to Na+: K+ ATPase activity in skeletal muscle
- Significant proportion ↑ blood lactate
  - Unrelated to poor tissue perfusion
  - Not respond to supranormal oxygen delivery
- Increased Na+: K+ ATPase activity
  - →↑lactate production under well-oxygenated conditions
  - Erythrocytes, vascular smooth muscle, neurons, skeletal muscle
Lactate

Enteric Bacteria

- Lactate produced by enteric bacteria
  Absorbed, produce lactic acidosis
  D-lactate
  - Endogenous lactate is L-lactate
- D-lactic acidosis
  Detection
  - Some assays for lactate only report L-lactate
  - Some assays report total lactate
  - Special D-lactate assays
    Will appear as unidentified anion if not assayed
- Metabolism
  Will be catabolized through L-lactate pathway
  Clearance is slower than D-lactate
Lactate

“High-octane” Fuel During Sepsis

- **High energy fuel for heart**
  - Allows maintenance of CO
  - Blocking lactate production:
    - Pronounced low flow state
    - Profound hypotension
  - Heart is a “metabolic omnivore”
    - Fatty acids (60-90%), glucose, lactate, and other

- **Energy for CNS during HI insults**
  - Protective – prevents lesions
  - Maintains CNS metabolism
  - High levels toxic to neurocytes

- **Lactate production**
  - Adaptive event in response to energetic crisis
SIG acidosis
Anion gap acidosis
Unmeasured anions

- Renal failure
- Ketoacidosis
  Starvation
  Metabolic errors
- Toxins
  Ethylene glycol
  Salicylates
- Sepsis/endotoxemia
  Lactic acidosis
  Other
- Liver disease
Non SIG acidosis
Non anion gap acidosis
SID acidosis

- **Hyperchloremic acidosis**
  \[^{\text{↑Cl}^-}\] relative to \[^{\text{Na}^+}\]
  Loss of cation relative to \[^{\text{Cl}^-}\]

- **Renal Acidosis – often some role**
  Renal response \(\rightarrow^{\text{↑Cl}^-}\) excretion in urine
  Kidney must be source of acidosis since
  - \[^{\text{↑plasma Cl}^-}\] rather than \[^{\text{↓plasma Cl}^-}\]

- **Extrarenal Acidosis (\[^{\text{↑Cl}^-}\])**
  From treatment with \[^{\text{Cl}^-}\] (NaCl)
  Lower GI tract cation loss without loss of \[^{\text{Cl}^-}\]
SID acidosis

• GI tract

Diarrhea

• Diarrhea fluid Na⁺ > Cl⁻ similar to plasma
• If treat with a NaCl → ↑Cl⁻ →↓SID
• If treat with SID balanced fluids
  Will not happen

Small intestinal disease
SID acidosis

• Iatrogenic
  TPN/PPN
  • Contains balance of weak anions (e.g. acetate) + Cl\(^-\)
    If acetate<< Cl\(^-\) then plasma Cl\(^-\) ↑ → ↓SID

Saline – dilutional acidosis

• Critical patient - already have lactic acidosis, can't change
  ventilation to compensate, have ↓A_TOT (↓albumin)
• Treated 5-10X plasma volume → significant acidosis
• Unlike normal patient treated with NaCl
Renal Acidosis

- Renal failure
  - Uncomplicated renal failure no acidosis
  - Hyperchloremic acidosis ↓SID
    - Na wasting > Cl excretion
    - Failure of Cl excretion without Na
  - Chronic ↑sulfates ↓SID
- Treat with NaHCO$_3$ → ↑SID
  - If Na$^+$ concentration is too high treat with Ca$^{++}$
  - But little ↑SID because of small normal range Ca
- Renal tubular acidosis
Renal Tubular Acidosis

- Defect in all types of RTA
  - Inability to excrete Cl⁻ in proportion to Na⁺
- RTA type I – distal
  - Impaired Na⁺ transport cortical collecting ducts
  - Treat NaHCO₃ → respond
  - K⁺ deficient/hyperkalemic form
Renal Tubular Acidosis

- **RTA type II - proximal**
  - Na$^+$ & K$^+$ reabsorption defect
    - Franconi Syndrome – glu, PO$_4$, urate, aa reabsorption defects
  - Treat Na HCO$_3$ → just ↑losses and not work

- **RTA type IV**
  - Aldosterone deficiency or resistance
  - ↑serum K and low urine pH (< 5.5)
  - Often caused by NSAIDs, heparin, K sparing diuretics
  - Discontinue drugs
Unexplained metabolic acidosis

- **Lactic acidosis**
  More acidotic than explained by lactate level

- **Sepsis**
  Acidosis without ↑ lactate
  - Could be D-lactate
  May be secondary to ↑ Cl⁻
  Unexplained anions released from liver
  - Normally liver clears unmeasured anions

- **Often ⅓ of acidosis is unexplained**
  Loss of Donnan equilibrium of plasma
  Capillary leak – loss of albumin from vascular space
  Cl⁻ moves into vascular space to balance loss
  Hyperchloremic acidosis with ↓ SID
Metabolic Alkalosis
Metabolic Alkalosis
Strong Ion Alkalosis
Increased SID

Strong Cations ↓H⁺

SID

Strong Anions ↓Cl⁻
Metabolic Alkalosis
Unidentified Cation Alkalosis
SIG > 0
Metabolic Alkalosis

- Metabolic alkalosis
  \[ \text{↑SID} \rightarrow \text{Results in ↓ free H}^+ \rightarrow \text{alkalosis} \]

- ↑SID
  - Loss of anions > cations
  - Diuretics
  - Renal disease
Metabolic alkalosis

- ↑SID

  Loss of Cl⁻ -- ↓anions
  - or from ↑cations (rare)

  Cl⁻ loss > Na

- Cl⁻ Responsive

- Cl⁻ Resistant
Potential Clinical Effects of Metabolic Alkalosis

- **Cardiovascular**
  - ↑Inotropy (Ca\(^++\) entry)
  - Altered coronary blood flow (↑/↓)
  - Digoxin toxicity

- **\(O_2\) Delivery**
  - ↑Oxyhemoglobin affinity
  - ↑2,3-DPG (delayed)
Potential Clinical Effects of Metabolic Alkalosis

- **Neuromuscular**
  - Neuromuscular excitability
  - Encephalopathy
  - Seizures

- **Metabolic Effects**
  - ↓K
  - ↓Ca
  - ↓PO4
  - Impaired enzyme function
Metabolic alkalosis
Cl Responsive

• Cl⁻ loss easily treated

Cl⁻ loss > Na⁺

Temporary loss – compensation

Not ongoing (Ucl low)

• Gastrointestinal

Reflux, Cl wasting diarrhea
Metabolic alkalosis
Cl Responsive

• Post diuretic
  Volume contraction $\rightarrow$↑aldosterone $\rightarrow$↑Na reabsorption
  But also ↑K and Cl⁻ loss $\rightarrow$ alkalosis

• Post chronic lactic acidosis
  ↓Cl⁻ as compensation for acidosis
  Lactic acidosis may resolve quickly
  Residual hypochloremic alkalosis

• Post hypercapnia – metabolic compensation
  Hypercapnea resolves quickly
  Residual hypochloremic alkalosis
Metabolic alkalosis
Cl Responsive

• Treatment
  Replace Cl with NaCl, KCl

• Dehydration usually present
  ↑ SID – corrected with saline
Metabolic Alkalosis
Cl Resistant

- Renal dysfunction
- Cl⁻ loss is ongoing (Ucl high)

Hormonal mechanisms
- Mineralocorticoid excess
- Primary/secondary hyperaldosteronism
- Cushing syndrome
- Liddle’s syndrome
- Bartter’s syndrome
- Excessive corticoids
- Excessive licorice intake (mimics aldosterone)

Ongoing diuretic use
Metabolic Alkalosis
Cl Resistant

• Only temporarily correct with Cl⁻ therapy
  Urine Cl⁻ > 20 mmol/l
  Saline therapy may temporarily correct SID

• Ongoing renal loss results in return ↑ SID
  ↑ Mineralocorticoid activity
Metabolic acid-base therapy

• If Na/Cl levels normal
  Don’t use Na/Cl in therapy

• If Na/Cl abnormal
  ↑ Na – NaHCO₃
  ↑ Cl – NaCl

• If ↑ lactate (↑ SIG, ↑ AG)
  ↑ metabolic clearance
  ↓ epinephrine levels
  ↓ hypermetabolism
  Don’t treat with NaHCO₃
  • After lactate ↓ - Na remains - ↑ SID
  • But pH < 7.20 liver may not clear lactate well