Acid – base balance

Summary of basic facts
Regulation of A-B balance
Pathophysiology of clinically important disorders

Acids vs. Bases
- definition: Bronsted-Lowry (1923)
- normal A:B ratio ~ 1:20

Henderson-Hasselbach equation:
\[ \text{pH} = 6.1 + \log \left( \frac{[\text{HCO}_3^-]}{0.03 \text{pCO}_2} \right) \]

- strength is defined in terms of the tendency to donate (or accept) the hydrogen ion to (from) the solvent (i.e. water in biological systems)

Why is pH so important?
- \([H^+] \sim \text{nmol/l}, [K^+, Na^+, Cl^-, HCO}_3^-] \sim \text{mmol/l};\) however, \([H^+]\) is crucial:
  - pH affects function of proteins
    - hydrogen bonds = 3-D structure = function
  - All the known low molecular weight and water soluble biosynthetic intermediates possess groups that are almost completely ionised at neutral pH
    - pH-dependent ionisation (i.e. charge) serves to an efficient intracellular trapping of ionised compounds within the cell and its organelles

- Exceptions:
  - macromolecules (proteins)
    - mostly charged anyway or size-trapping or hydrophobic
  - lipids
    - those needed intracellularly are protein-bound
  - waste products
    - excretion is desirable
The most important pH for the body is the intracellular pH

- Intracellular pH is maintained at about the pH of neutrality (~6.8 at 37°C) because this is the pH at which metabolite intermediates are all charged and trapped inside the cell.

- Extracellular pH is higher by 0.5 to 0.6 pH units and this represents about a 4-fold gradient favouring the exit of hydrogen ion from the cell to maintain it at a stable value because of the powerful effects of intracellular [H+] on metabolism

  - maintaining a stable intracellular pH by:
    - ‘Intracellular buffering’ (chemical, metabolic, organelles)
    - Adjustment of arterial pCO2
    - Loss of fixed acids from the cell into the extracellular fluid

pN → [H+] = [OH−]  

pN=7.0 at 25°C for pure H2O  
pN=6.8 at 37°C in cell

pH is constantly “impaired” by metabolism

- production of metabolic acids
  - “volatile” acids (CO2 resp. H2CO3)
    - Intermediate metabolism of substrates (oxidation)
      - CO2 + H2O → H2CO3

- “fixed” acids
  - strong anorganic acids
    - metabolism of proteins resp. PA
      - sulphonic (Met, Cys)
      - hydrochlorous (Arg, Lys)
  - lactate
    - anaerobic glycolysis
  - keton bodies
    - metabolism of fatty acids → ketogenesis → acetoacetate and hydroxybutyrate

- regulation of pH
  - intracell. a extracell. buffers
  - lungs - respiration (CO2)
  - kidneys
    - reabsorption of HCO3−
    - excretion of H+

Chemical buffers and other types of H+ buffering

- (1) proteins (amphoteric)
  - H+ and CO2 diffuse across plasma membrane and are buffered
    - ECF - albumin
      - haemoglobin is strictly speaking ICF, but...!!
    - ICF - cellular proteome

- (2) inorganic buffers
  - ECF - carbonic acid / bicarbonate
    - H2CO3 / HCO3−
  - ICF - phosphoric acid / hydrogen phosphate
    - H3PO4 / H2PO4− / HPO42−

- (3) transcellular exchange H+/K+
  - changes of ABB influence potassium balance and vice versa !!!
  - hormonal effects!!
Organs involved in the regulation of ABB

- Equilibrium with plasma
- High buffer capacity
- Excretion of CO₂ by alveolar ventilation: minimally 12,000 mmol/day
- Respiratory centre reacts in minutes, maximum compensation in 12 – 24 hod, then decline of sensitivity
- Reabsorption of filtered bicarbonate: 4,000 to 5,000 mmol/day
- Excretion of the fixed acids (acid anion and associated H+):
  - about 100 mmol/day
- CO₂ production from complete oxidation of substrates:
  - 20% of the body's daily production
  - such as lactate, ketones and amino acids
- Metabolism of organic acids
- Metabolism of ammonium
  - conversion of NH₄⁺ to urea in the liver consumes HCO₃⁻
- Production of plasma proteins
  - esp. albumin contributing to the anion gap
- Bone inorganic matrix consists of hydroxyapatite crystals (Ca₁₀(PO₄)₆(OH)₂]
  - bone can take up H⁺ in exchange for Ca²⁺, Na⁺ and K⁺ (ionic exchange)
  - release of HCO₃⁻, CO₃⁻ or HPO₄²⁻

Regulation by resp. system - CO₂

- differences in the stimulation of respiration by pCO₂ ([H⁺] resp. in the CSF) and/or pO₂<60mmHg
- changes of alveolar ventilation
- disorders:
  - acidemia
    - → respiratory centre of the brain
    - → ↑ alveolar ventilation
    - → ↓ CO₂
  - alkalemia
    - → respiratory centre of the brain
    - → ↓ alveolar ventilation
    - → ↑ CO₂

Respiratory centre

- long-lasting respiratory acidosis (↑PaCO₂) decreases sensitivity of resp.
  - centre to PaCO₂ and PaO₂ becomes the main regulator
- administration of oxygen therapeutically can sometimes lead to worsening of resp.
  - acidosis or even to respiratory arrest !!!

Renal system – fixed H⁺ & HCO₃⁻

- Proximal tubular mechanisms:
  - reabsorption of HCO₃⁻ filtered at the glomerulus
    - carboanhydrase
    - NHE-3 exchanger (reabsorption of HCO₃⁻ is coupled with reabsorption of Na⁺)
    - production of NH₄⁺
      - from glutamine in prox. tubule with parallel formation of HCO₃⁻
      - glutamine is a way of body to dispose of nitrogen (in liver)
      - most of NH₄⁺ recycles in the renal medulla
  - Distal tubular mechanisms:
    - net excretion of H⁺
      - normally 70mmol/day
      - max. 700mmol/day
      - together with proximal tubule excretion of H⁺ could increase up to 1000x!!! (↓pH of urine down to 4.5)
    - reaction with HPO₄²⁻ - formation of “titratable acidity” (TA)
    - addition of NH₄⁺ to luminal fluid
    - reabsorption of remaining HCO₃⁻
Regulation of ABB in different parts of the nephron

Na+/K+ ATP-ase
- Electrogenic (ratio 3 Na+:2 K+)
- Energy for secondary-active transports with Na+

Assessment of A-B balance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arterial blood (interval)</th>
<th>Venous blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.40</td>
<td>7.33 - 7.43</td>
</tr>
<tr>
<td>H+ (nmol/l)</td>
<td>40</td>
<td>36 - 44</td>
</tr>
<tr>
<td>pCO₂ (mmHg/kPa)</td>
<td>40 / 5.3</td>
<td>35 - 45 / 5.1 - 5.5</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/l)</td>
<td>25</td>
<td>22 - 26</td>
</tr>
<tr>
<td>BE</td>
<td>±2</td>
<td>24 - 28</td>
</tr>
<tr>
<td>AG (mEq/l)</td>
<td>12</td>
<td>10 - 14</td>
</tr>
<tr>
<td>Hb saturation (%)</td>
<td>95</td>
<td>80 - 95</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>95</td>
<td>80 - 95</td>
</tr>
</tbody>
</table>

Disorders of A-B balance
- Acidosis vs. alkalosis: abnormal condition lowering or raising arterial pH
  - Before activation of compensatory changes in response to the primary aetiopathological factor
- Simple vs. mixed A-B disorders: single vs. multiple aetiopathological factors
- Disorders are defined according to their effect on pH of ECF
  - Acidaemia: arterial pH<7.36 (i.e. [H+]>44 nM)
  - Alkalaemia: arterial pH>7.44 (i.e. [H+]<36 nM)
- Primary cause → buffers → compensation → correction
**Causes**

- **Respiratory**
  - abnormal processes which tend to alter pH because of a primary change in $p_{CO_2}$ levels
    - acidosis
    - alkalosis
  - buffering
    - predominantly intracellular proteins
  - compensation
    - hyperventilation
      - typically limited, hyperventilation often cause of disorder
    - renal
      - delayed (days)

- **Metabolic**
  - abnormal processes which tend to alter pH because of a primary change in $[HCO_3^-]$ or $pH$
    - acidosis
    - alkalosis
  - buffering
    - predominantly bicarbonate system
  - compensation
    - hyperventilation
      - rapid (min - hrs)
    - renal
      - delayed (days)

**Respiratory acidosis (RAC)**

- primary disorder is a ↓pH due to ↑$PaCO_2$ (>40 mmHg), i.e. hypercapnia

  - time course:
    - acute (↓pH)
    - chronic (↓pH or normalisation of pH)
      - renal compensation – retention of $HCO_3^-$; 3-4 days

- causes of RAC:
  - decreased alveolar ventilation (most cases)
    - the defect leading to this can occur at any level in the respiratory control mechanism
    - the degree of hypoxemia corresponds with degree of alveolar hyperventilation
    - enrichment of %O$_2$ in inhaled air corrects solely “pure hypoventilation” !!!
  - presence of excess CO$_2$ in the inspired gas
    - re-breathing of CO$_2$-containing expired gas
    - addition of CO$_2$ to inspired gas
    - insufflation of CO$_2$ into body cavity (e.g. for laparoscopic surgery)
  - increased production of CO$_2$ by the body
    - malignant hyperthermia, sepsis

**Pathologic effects of hypercapnia**

- CO$_2$ rapidly diffuses across membranes
  - depression of intracellular metabolism

- Extreme hypercapnia
  - cerebral anaesthetic effects
    - (p$CO_2$>100mmHg)

- Effect of hypoxemia

**RA - inadequate alveolar ventilation**

- Central respiratory depression & other CNS problems
  - drug depression of respiratory centre (e.g. by opiates, sedatives, anaesthetics)
  - CNS trauma, infarct, haemorrhage or tumour
  - hypoventilation of obesity (e.g. Pickwick syndrome)
  - cervical cord trauma or lesions (at or above C4 level)
  - high central neural blockade
  - poliomyelitis
  - tetanus
  - cardiac arrest with cerebral hypoxia

- Nerve or muscle disorders
  - Guillain-Barre syndrome
  - Myasthenia gravis
  - muscle relaxant drugs
  - toxins e.g. organophosphates, snake venom
  - various myopathies

- Lung or chest wall defects
  - acute on COPD
  - chest trauma -confusion, haemothorax
  - pneumothorax
  - diaphragmatic paralysis
  - pulmonary oedema
  - adult respiratory distress syndrome
  - restrictive lung disease
  - aspiration

- Airway disorders
  - upper airway obstruction
  - laryngospasm
  - bronchospasm / asthma

- External factors
  - Inadequate mechanical ventilation

- An arterial $pCO_2$>90 mmHg is not compatible with life in patients breathing room air:
  - $PaO_2 = (0.21 \times (760 - 47)) - 90/0.8 = 37$ mmHg
RAC – compensation and correction

- **Acute RAC - buffering only!**
  - About 99% of this buffering occurs intracellularly
  - Proteins (haemoglobin and phosphates) are the most important intravascular buffers for CO₂, but their concentration is low relative to the amount of carbon dioxide requiring buffering.
  - The bicarbonate system is not responsible for any buffering of a respiratory acid-base disorder.
  - The system cannot buffer itself.
  - Efficiency of compensatory hyperventilation is usually limited.

- **Chronic RAC - renal compensation**
  - Bicarbonate retention
  - Takes 3 or 4 days to reach its maximum
  - \( \text{PaCO}_2 \rightarrow \text{H}^+ \) secretion into the lumen:
    - \( \text{Na}^+ \) reabsorption in exchange for \( \text{H}^+ \)
    - \( \text{NH}_4 \) production and secretion to 'buffer' the \( \text{H}^+ \) in the tubular lumen, parallel regeneration of HCO₃⁻.

- **RAC treatment**
  - The pCO₂ rapidly returns to normal with restoration of adequate alveolar ventilation.
  - Rapid fall in pCO₂ (especially if the RA has been present for some time) can result in:
    - Severe hypotension
    - "Post hypercapnic alkalosis"
Pathologic effects of MAC

- **Respiratory**
  - hyperventilation
  - shift of haemoglobin dissociation curve to the right
- **Cardiovascular**
- **Others**
  - increased bone resorption (chronic acidosis only)
  - shift of K⁺ out of cells causing hyperkalemia

Some effects of MAC are opposite

- **Cardiovascular system**
  - pH>7.2 - effect of SNS stimulation dominates (catecholamines)
  - pH<7.2
    - direct inhibitory effect of [H⁺] on contractility
    - vasodilatory effect of [H⁺]
- **Hb dissociation curve**
- **Plasma [K⁺] reflects**
  - K⁺/H⁺ exchange
  - glomerular filtration rate
    - e.g. renal failure
    - osmotic diuresis
      - e.g. ketoacidosis

Common types of MAC - ketoacidosis

- **Contributing disorders**
  - increased lipolysis in adipose tissue – mobilisation of NEFA
  - increased production of keton bodies from acetyl CoA (lipolysis of TG) in liver (β-hydroxybutyrate, acetoacetate, acetone)
    - their mutual ratio depends on ration NADH/NAD⁺
- **Ketoacidosis is a consequence of**
  - ↓ insulin/glucagon
  - ↑ catecholamines, ↑ glucocorticoids
- **(1) Diabetic**
  - hyperglycaemia + precipitating factors (stress, infection)
    - lipolysis (insulin, catecholamines) – NEFA – dysregulation of NEFA metabolism in liver (insulin, glucagon) – ↑NEFA oxidation –↑acetyl CoA – ketogenesis
    - clin. manifestation results from hyperglycaemia and ketoacidosis
- **(2) Alcoholic**
  - typically chron. alcoholic several days after last binge, starving
    - hepatic metabolism effective enough to prevent prolonged acidosis
  - impaired metabolism of lactate
    - type A = hypoxic
      - shock (hypovolemic, distributive, cardiogenic), hypotension, anemia, heart failure, liver failure, malignancy, ... most often in combination !!!
    - type B = inhibition of complete metabolism of lactate
      - drugs – biguanids (inhibition of ox. phosphorylation in mitochondria)
- **(3) Starvation**

Common types of MAC - lactic acidosis

- **Under normal circumstances entire lactate recycles**
  - lactate - pyruvate - complete oxidation
  - gluconeogenesis (60% liver, 30% kidney)
  - renal threshold (5mmol/l) guarantee complete reabsorption under normal circumstances
- **Lactic acidosis**
  - increased production
    - physical exercise, convulsions
  - impaired metabolism of lactate
    - type A = hypoxic
      - shock (hypovolemic, distributive, cardiogenic), hypotension, anemia, heart failure, liver failure, malignancy, ... most often in combination !!!
    - type B = inhibition of complete metabolism of lactate
      - drugs – biguanids (inhibition of ox. phosphorylation in mitochondria)
Metabolic alkalosis (MAL)

- **Pathophysiology (according to the event, parallel change of circulating volume):**
  - (A) hypovolemic MAL - compensatory retention of Na in kidney (aldosterone) leads to increased excretion of H+
    - loss of acidic ECF - prolonged vomiting or gastric juice drainage
    - overuse of diuretic (apart from acetazolamide and K sparing diuretics)
    - congenital hypochloremia
    - some diarrhoeas (secretory type - CI losses)
    - diabetes insipidus
    - Bartter’s syndrome
  - (B) normo-/hypervolemic MAL
    - posthypercapnic
      - increased alkali intake (antacids - NaHCO3, CaCO3)
      - primary hyperaldosteronism
      - secondary hyperaldosteronism (e.g. renovascular hypertension)
      - Cushing syndrome
      - liver failure (tertiary hyperaldosteronism) combined with MAL due to stimulation of resp. centre by liver toxic metabolites
  - **compensation**
    - buffers
      - retention of pCO2 by stimulation of resp. centre
      - however limited - pCO2 = 55mmHg hypoxia becomes regulatory parameter
    - renal compensation limited as well because kidney either pathogenetically contributes to MAL (B) or counteracts hypovolemia (A) – circulus vitiosus

- **↑pH due to ↑HCO3:**
  - loss of ECF
    - vomiting
    - hypovolemia

- **Metabolic alkalosis**