SERUM ELECTROLYTE ANIONS

Chloride

- The major extracellular anion
- Function in body:
  - Maintaining osmolality
  - Blood volume and
  - Electric neutrality
- Cl is usually shifted according to Na and bicarbonate
- Excess chloride in the body is excreted in urine and sweat, excessive sweating will induce the release of aldosterone which will conserve Na and Cl

Chloride

- Chloride maintains electrical neutrality in two ways:
- Na is reabsorbed along with Cl in the proximal tubules. Na reabsorption is limited by the amount of Cl- available
- Electroneutrality is also maintained by chloride through the chloride shift.
  - Carbon dioxide generated by cellular metabolism within the tissue diffuses out into both the plasma and the red cells
  - In the red cell, CO2, forms carbonic acid (H2CO3), which splits into H+ and HCO3- (bicarbonate).
  - Deoxyhemoglobin buffers H+, whereas the HCO3- diffuses out into the plasma and Cl diffuses into the red cell to maintain the electric balance of the cell.

Chloride applications

- Chloride disorders are often the result of the same causes that disturb Na levels because chloride passively follows Na
- There are a few exceptions.
  - Hyperchloremia may also occur when there is an excess loss of bicarbonate as a result of GI losses, RTA or metabolic acidosis
  - Hypochloremia may occur with excessive loss of chloride from prolonged vomiting, diabetic ketoacidosis, aldosterone deficiency or salt-losing renal diseases.
  - A low serum level of chloride may be encountered in conditions associated with high serum bicarbonate concentrations such as compensated respiratory acidosis or metabolic alkalosis.

Determination of the chloride

- Specimen: serum or plasma, whole blood samples, urine (24-hr) or sweat may be used
- Lithium heparin is the anticoagulant of choice.
- Hemolysis does not cause significant change in serum or plasma values as a result of decreased levels of intracellular chloride (marked hemolysis, decrease due to dilutional effect).
- Methods: there are several methodologies includes:
  - ISE (most commonly used where an ion-exchange membrane is used to selectively bind Cl ions)
  - Amperometric coulometric titration
  - Mercurimetric titration
  - Colorimetry
- Amperometric coulometric titration method using coulometric generation of silver ions (Ag which combine Cl to quantitate the Cl ion concentration
- $$Ag^+ + Cl^- \longrightarrow AgCl$$

Reference range

TABLE 15-10 REFERENCE RANGES FOR CHLORIDE

Plasma, serum	98–107 mmol/L
Urine (24-h)	110–250 mmol/day, varies with diet

Bicarbonate

- Is the second most abundant anion in the ECF
- The total CO2 comprises the bicarbonate (90%), carbonic acid and dissolved CO2 so total CO2 measurement is indicative of HCO3- measurement
- Bicarbonate is the major buffering system in the blood where carbonic anhydrase in RBCs converts CO2 and H2O to carbonic acid

$$CO_2 + H_2O \xleftrightarrow{CA} H_2CO_3 \xleftrightarrow{CA} H^+ + HCO_3^-$$

- Bicarbonate diffuses out of the cells in exchange for chloride to maintain ionic charge neutrality within the cell

Bicarbonate regulation

- Most of the filtered bicarbonate ion is reabsorbed in the kidneys (85% in proximal tubules and 15% in the distal) in the form of CO_2 (due to low permeability of tubules to bicarbonate)
- Normally nearly all the bicarbonate ions are reabsorbed from the tubules, with little lost in the urine
- When bicarbonate ions are filtered in excess of hydrogen ions available, almost all excess HCO_3^- flows into the urine.
- In alkalosis, with relative increase in bicarbonate ion compared to CO_2, the kidneys increase excretion of HCO_3^- into the urine, carrying along a cation such as sodium. This loss of HC3O- from the body helps correct pH
- In acidosis, the excretion of H into the urine is increased and HCO_3^- reabsorption is virtually complete

Clinical applications

- Acid-base imbalances cause changes in bicarbonate and CO2 levels. A decreased bicarbonate/ CO2 occurs in metabolic acidosis leads to exhalation of CO2 by the lungs (hyperventilation), which lowers pCO2.
- Elevated total CO2 concentrations occur in metabolic alkalosis as bicarbonate is retained, often with increased pCO2, as a result of compensation by hypoventilation.
- Typical causes of metabolic alkalosis include:
  - Severe vomiting
  - Hypokalemia
  - Excessive alkali intake

Method

- Specimen: venous serum or plasma.
- Serum or lithium heparin plasma is suitable for analysis.
- The sample is capped until the serum or plasma is separated and the sample is analyzed immediately
- If the sample is left uncapped before analysis, CO_2 escapes. Levels can decrease by 6 mmol/L per hour
- Two common methods are ISE and an enzymatic method.
    - ISE for measuring total CO_2, uses an acidic reagent to convert all the forms CO_2 to CO_2 gas and measured by a pCO_2 electrode
    - The enzyme method alkalinizes the sample to convert all forms of CO_2 to HCO_3^-.

Method

- HCO3 is used to carboxylate phosphoenolpyruvate (PEP) of phosphoenolpyruvate (PEP) carboxylase, which catalyzes the formation of oxaloacetate.

$$\text{Phosphoenolpyruvate} + HCO_3^- \xrightarrow{\text{PEP carboxylate}} \text{Oxaloacetate} + H_2PO_4^- \quad \text{(Eq. 15-4)}$$

- This is coupled to the following reaction, in which NADH is consumed as a result of the action of malate dehydrogenase (MDH)

$$\text{Oxaloacetate} + \text{NADH} + H^+ \xrightarrow{\text{MDH}} \text{Malate} + \text{NAD}^+ \quad \text{(Eq. 15-5)}$$

- The rate of change in the absorbance of NADH is proportional to the concentration of HCO3-

Reference ranges

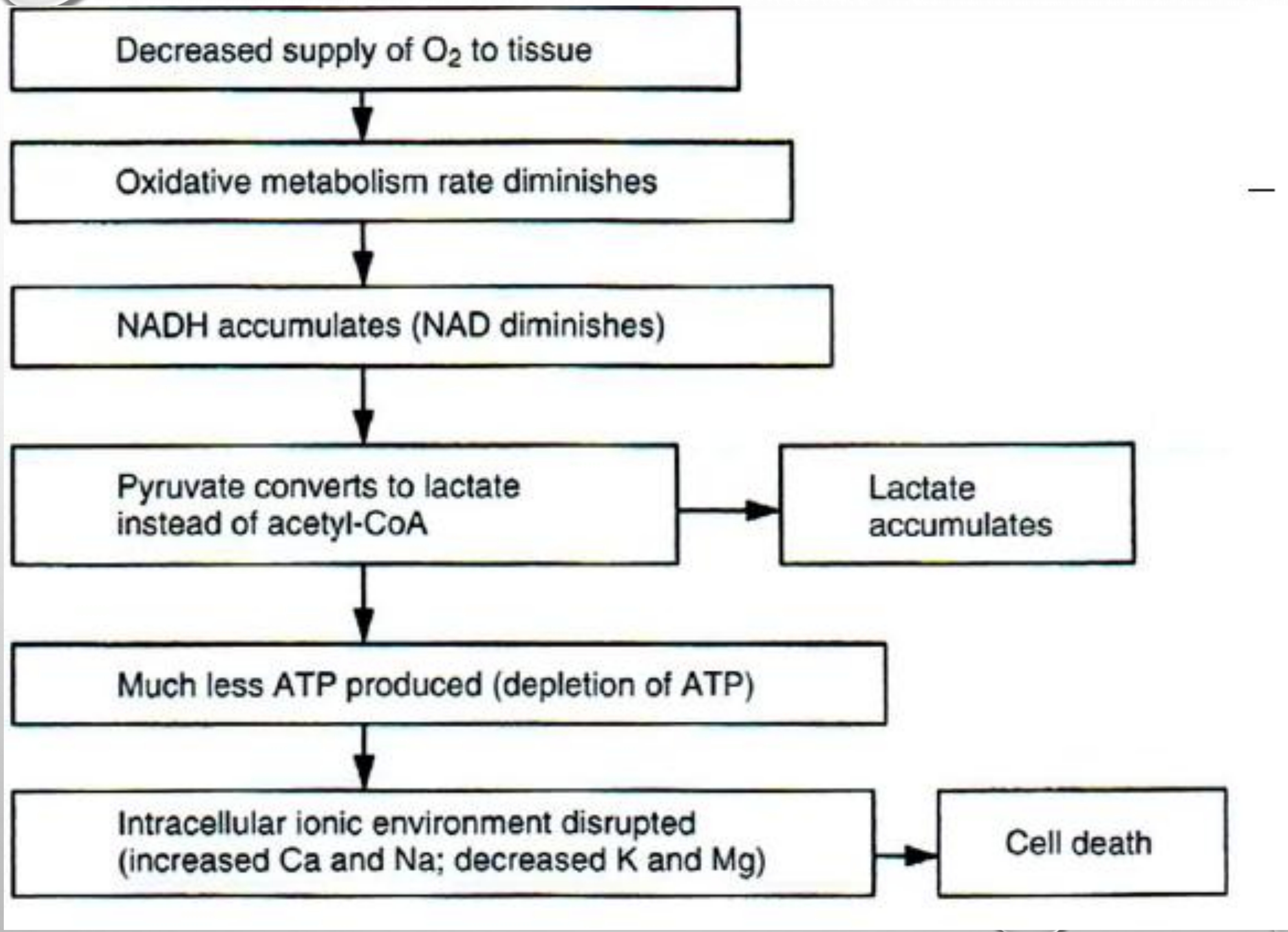
- Carbon dioxide, venous 23-29 mmol/L (plasma, serum).

Lactate

- Lactate is a by-product of an emergency mechanism that produces a small amount of ATP (2 moles)

- Under hypoxic conditions, acetyl CoA formation does not occur and NADH accumulates, favoring the conversion of pyruvate to lactate through anaerobic metabolism.

- The accumulation of excess lactate in blood is an early sensitive and quantitative indicator of the severity of oxygen deprivation (more than pH)


Decreased supply of O_2 to tissue
Oxidative metabolism rate diminishes
NADH accumulates (NAD diminishes)
Pyruvate converts to lactate instead of acetyl-CoA
Lactate accumulates
Much less ATP produced (depletion of ATP)
Intracellular ionic environment disrupted (increased Ca and Na; decreased K and Mg)
Cell death

Regulation

- It is not regulated as with potassium and calcium
- As oxygen delivery decreases below a critical level, blood lactate concentration rise rapidly and indicate tissue hypoxia earlier than pH
- The liver is the major organ for removing lactate by converting lactate back to glucose by a process called gluconeogenesis

Clinical application

- Measurement of blood lactate are useful for metabolic monitoring in critically ill patients, for indicating the severity of the illness, and patient prognosis

There are two types of lactic acidosis:

  - Type A is associated with hypoxic conditions, such as shock, myocardial infarction, severe congestive heart failure, pulmonary edema, or severe blood loss

  - Type B is of metabolic origin, such as with diabetes mellitus, severe infection, leukemia, liver or renal disease, and toxins (ethanol, methanol, or salicylate poisoning).

Determination of lactate

- Special care should be practiced when collecting and handling specimens for lactate levels
- A tourniquet should not be used because venous stasis will increase lactate levels
- If a tourniquet is used, blood should be collected immediately and the patient should not exercise the hand before and during collection
- After sample collection, glucose is converted to lactate by a way of anaerobic glycolysis and should be prevented:
  - Heparinized blood may be used but must be delivered on ice and the plasma must be quickly separated
  - Iodoacetate or fluoride will inhibit glycolysis without affecting coagulation

Method

- Current enzymatic methods make lactate determination readily available.
- The most commonly used enzymatic method uses lactate oxidase to produce pyruvate and H2O2.

$$\text{Lactate} + O_2 \xrightarrow{\text{Lactate oxidase}} \text{pyruvate} + H_2O_2$$

- One of two couple reactions may then be used. Peroxidase may be used to produce a colored chromogen from H2O2

$$H_2O_2 + \text{H donor} + \text{chromogen} \xrightarrow{\text{Peroxidase}} \text{colored dye} + 2H_2O$$

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Reference range

ENZYMATIC METHOD, PLASMA	
Venous	0.5–2.2 mmol/L (4.5–19.8 mg/dL)
Arterial	0.5–1.6 mmol/L (4.5–14.4 mg/dL)
CSF	1.1–2.4 mmol/L (10–22 mg/dL)

Anion gap (AG)

- Routine measurement of electrolytes usually involves only Na^+, K^+, Cl^-, and HCO_3^-
- These values may be used to approximate the anion gap (AG), which is the difference between unmeasured anions and unmeasured cations.
- There is never a “Gap” between total cationic charges and anionic charges
- AG is useful in indicating an increase in one or more of the unmeasured anions in the serum and also in the form of quality control for the analyzer used to measure these electrolytes.

Anion gap (AG)

- There are two commonly used methods for calculating the anion gap

$$AG = Na^{+} - (Cl^{-} + HCO_3^{-})$$

- With a reference range of 7-16 mmol/L
- The second method:

$$AG = (Na^{+} + K^{+}) - (Cl^{-} + HCO_3^{-})$$

- It has a reference range of 10-20 mmol/L

Anion gap (AG)

- An elevated anion gap may be caused by:
  - Uremia/renal failure, which leads to PO4-3 and SO4-2 retention
  - Ketoacidosis, as seen in cases of starvation or diabetes
  - Methanol, ethanol, ethylene glycol poisoning, or salicylate
  - Lactic acidosis
  - Hypernatremia
  - Instrument error

CASE STUDY 15-2

A 60-year-old man entered the emergency department after 2 days of "not feeling so well." History revealed a myocardial infarction 5 years ago, when he was prescribed digoxin. Two years ago, he was prescribed a diuretic after periodic bouts of edema. An electrocardiogram at time of admission indicated a cardiac arrhythmia. Admitting lab results are shown in Case Study Table 15-2.1.

Questions

1. Because the digoxin level is within the therapeutic range, what may be the cause for the arrhythmia?
2. What is the most likely cause for the hypomagnesemia?
3. What is the most likely cause for the decreased potassium and ionized calcium levels?
4. What type of treatment would be helpful?

CASE STUDY TABLE 15-2.1 LABORATORY RESULTS

VENOUS BLOOD
Digoxin: 1.4 ng/mL, therapeutic 0.5–2.2 (1.8 nmol/L, therapeutic 0.6–2.8)
Na^+: 137 mmol/L
K^+: 2.5 mmol/L
Cl^-: 100 mmol/L
HCO_3^-: 25 mmol/L
Mg^{2+}: 0.4 mmol/L
Ion/free Ca^{2+}: 1.0 mmol/L

Na	135-145
K	3.4-5.0
Cl	98-107
HCO3	23-29
Mg	0.63-1.0
Ca/ionized	1.16-1.32