Key Points:

- Normal production and consumption of lactate produces H+ and HCO3- in equal amounts, preventing changes to pH
- Hypoxia favors pyruvate conversion to lactate and prevents normal lactate metabolism, resulting in H+ and acidemia
- Treatment of lactic acidosis involves correction of underlying disease and in rare cases (pH < 7.2 or 7.1) HCO3- therapy

Lactic acid is completely dissociated at physiologic pH.

- Two categories
    - Type A (hypoxic)
        - Normal mitochondrial function but inadequate DO2
    - Type B (non hypoxic)
        - Adequate DO2
        - Defective mitochondrial oxidative function and abnormal carbohydrate metabolism
        - Congenital mitochondrial myopathies have been reported in dogs

Box 10-2 Causes of L-Lactic Acidosis*

Type A: hypoxic
Increased oxygen demand
- Severe exercise
- Convulsions

Decreased oxygen availability
- Reduced tissue perfusion
  - Cardiac arrest, cardiopulmonary resuscitation
  - Shock
  - Hypovolemia
  - Left ventricular failure
  - Low cardiac output
  - Acute pulmonary edema
- Reduced arterial oxygen content
  - Hypoxemia ($Po_2 \leq 30$ mm Hg)
  - Extremely severe anemia (packed cell volume < 10%)

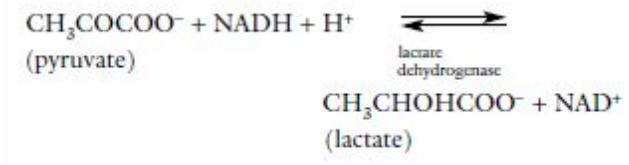
Type B: nonhypoxic
Drugs and toxins
- Phenformin
- Salicylates
- Ethylene glycol
- Many others[130]

Diabetes mellitus
Liver failure
Neoplasia (e.g., lymphosarcoma)
Sepsis
Renal failure
Hypoglycemia
Hereditary defects
- Mitochondrial myopathies
- Defects in gluconeogenesis

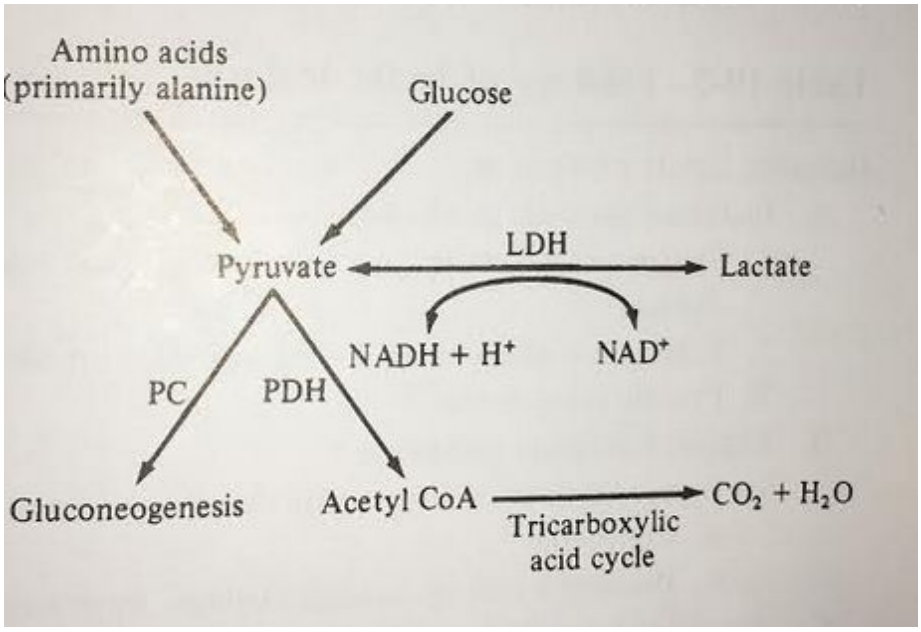
*D-Lactic acidosis occurs with short bowel syndrome in humans and has been observed in cats fed propylene glycol.[40,41]

Lactate

- End product of metabolism that allows for regeneration of cytosolic NAD+ during anaerobic metabolism
  - Will then go on to be reoxidized to pyruvate



  - Equilibrium favors lactate 10:1 over pyruvate



PC = Pyruvate carboxylase
PDH = Pyruvate dehydrogenase
LDH = Lactate dehydrogenase

- Under aerobic conditions, NADH -> NAD+. Pyruvate -> Acetyl CoA -> Krebs cycle
- Anaerobic conditions: oxidative pathways are disrupted and NAD+ must be replenished by reduction of pyruvate to lactate in cytosol.
- There will be an accumulation of NADH which will shift the equation further in favor of Pyruvate into lactate
    - Gut and skeletal muscles produce majority of lactate
    - LIver and kidneys are main consumers of lactate for gluconeogenesis (liver mostly)
    - Protons are consumed when lactate is metabolized

Gluconeogenesis

$$2CH_3CHOHCOO^- + 2H^+ \rightarrow C_6H_{12}O_6$$

Oxidative metabolism

$$CH_3CHOHCOO^- + H^+ + 3O_2 \rightarrow 3CO_2 + 3H_2O$$

    - Lactate + 3O2 -> HCO3- + 2CO2 + 2H2O
    - 2Lacate +2H2O + 2CO2 -> 2HCO3- + glucose
-
    - In severe anaerobic situations (PaO2 < 30mmHg) liver cannot process lactate and begins to produce lactate in acidic environments

L and D lactate

- Different isomers
    - L is mammal form

        - D is produced mainly by bacteria and is elevated in short bowel syndrome in people due to bacterial overgrowth
            - Possible in cats and dogs, not commonly reported

Exercise

- Lactate concentration in racing greyhounds increased up to 29mEq/L but returned to normal after around 3 hours

Lymphoma

- Lymphoma (stage III or IV) dogs have inappropriate lactate handling and are disposed to worse hyperlactatemia than healthy dogs and may even have increased lactate transiently after LRS administration
    - Remission did not improve hyperlactatemia in these dogs

Consequences of acidosis:

- Vasodilation
- Decreased myocardial contractility
- Proarrhythmic state
- Resistance to catecholamines

Treatment:

- Treat underlying disease
- Bicarbonate therapy if pH is <7.1-7.2 and if not resolving with other treatment
    - Other therapies
        - THAM
        - Carbicarb
    - Adverse effects of Biacarb:
        - Hypernatremia
            - Hypervolemia
        - Paradoxic cerebral acidosis
            - Only CO_2 can cross BBB
        - Overshoot alkalosis
        - Decreased Ca++
            - From increased binding to protein
        - Hypokalemia
            - From H^+ <-> K^+ exchanging from cells

Questions:

1. Accumulation of _____ in the cytosol shifts the equilibrium of lactate and _____ in favor of more production of lactate
2. Name 3 adverse effects of acidosis
3. Name 4 adverse effects of bicarbonate administration

Answers

1. Accumulation of NADH+ in the cytosol shifts the equilibrium of lactate and Pyruvate in favor of more production of lactate
2. Name 3 adverse effects of acidosis
    a. Vasodilation
    b. Decreased myocardial contractility
    c. Proarrhythmic state
    d. Resistance to catecholamines
3. Name 4 adverse effects of bicarbonate administration
    a. Hypernatremia
    b. Volume overload
    c. Cerebral acidosis
    d. Decreased Ca++
    e. Hypokalemia