LACTIC ACIDOSIS
TYPE A & B

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OBJECTIVES

• The attendee will be able to describe and distinguish the differences between Type A and Type B Lactic Acidosis.

• Attendees will have the ability to discuss the key principles respiratory therapist need to possess to response appropriately when faced with lactic acidosis.
LACTATE OR LACTIC ACID
LACTIC ACID

The Benefits of Lactic Acid
Lactic acid leads to softer, smoother skin by:

- Increasing cell turnover
- Stimulating cell removal
- Improving skin’s natural moisture factor
- Stimulating collagen renewal for firmness
Physicians are paying more attention to serum lactate levels in hospitalized patients than in the past. Elevated lactate levels are associated with tissue hypoxia, hypoperfusion, and a number of other serious conditions. Therefore, confusion can arise as to how to interpret elevated lactate levels. This review will discuss the mechanisms underlying lactic acidosis, its prognostic implications, and its use as a therapeutic target in treating patients' serious disorders.
AEROBIC METABOLISM

Glucose is broken down in the cytoplasm of the cell.

Glycolysis (ADP and NAD+ act on glucose) end result is pyruvate, ATP, NADH, Hydrogen, H₂O.

Acetyl CoA is produced (Krebs Cycle) due to pyruvate entering the mitochondria.

High energy electrons are transported through this last stage converting glucose to energy (38 ATP), leaving CO₂ and H₂O as byproducts.
ANAEROBIC METABOLISM

Glycolysis occurs without the use of oxygen.

Little energy is converted (only 2 ATP) leaving lactate as a byproduct.

This lactate converted to pyruvate.

Most pyruvate can be converted back to glucose (gluconeogenesis) via the liver and kidneys.
AEROBIC & ANAEROBIC METABOLISM

Glucose → Glycolysis → 2 Pyruvate

Aerobic metabolism:
- 2 Pyruvate → Acetyl CoA
- Acetyl CoA → Krebs cycle
- Krebs cycle → High-energy electrons
- Electron transport system → 34 ATP
- 34 ATP + 2 ADP → 34 ATP
- 34 ATP + 2 ADP → CO₂ + H₂O

Anaerobic metabolism:
- 2 Pyruvate → 2 Lactate

Gluconeogenesis:
- Glucose → Gluconeogenesis
LACTATE PRODUCTION

• Lactate (or Lactic Acid) is produced from pyruvate as an end product of glycolysis under anaerobic conditions (anaerobic respiration).
• Lactate is produced in most tissues in the body (primarily skeletal muscle, the brain, intestine, RBC’s – which can not be metabolized further)
• During times of stress, lactate is also produced in the lungs, WBC’s, and splanchnic organs.
LACTATE CLEARANCE

• Most lactate in the blood is cleared by the liver, where it is the substrate for gluconeogenesis.
• Small amounts are also cleared by the kidneys and heart.
• Lactate is converted back to glucose in the liver by way of the Cori Cycle.
• The Cori Cycle (also known as the Lactic Acid Cycle) refers to lactic acid produced by anaerobic metabolism in the muscles.
• This lactate is moved to the liver, converted back to glucose, which then is returned to the muscles, helping to produce ATP (key during fasting, starvation, strenuous exercise).
CORI CYCLE

Glucose → 6 ATP → 2 Pyruvate → 2 Lactate → Liver

Muscle → Glucose → 2 ATP → 2 Pyruvate → 2 Lactate
LACTATE LEVELS

• Basal lactate production is approximately 0.8 mmol/kg (IBW) or 1500 mmol/day
• Normal arterial blood lactate level = 0.620 mmol/L
• Normal venous blood lactate level = 0.997 mmol/L
• Normal lactate levels < 2.0 mmol/L
• Intermediate Level Range: 2 – 4 mmol/L
• High levels: > 4 mmol/L (hyperlactatemia)
• 1 mmol/L = 9 mg/dL
LACTATE CLEARANCE

• The higher the lactate level and the slower the rate of normalization (lactate clearance), the higher the risk of the death for that individual.

• Lactate disposal is achieved either conversion to pyruvate which is eliminate by the liver or elimination in urine by the kidney.

• Lactate production must equal what is being removed!!!!

• Exercise may temporarily upset this balance (during severe exercise blood lactate levels may rise in excess of 20 mmol/L) but due to rapid lactate disposal this is not a issue.
HYPERLACTATEMIA
LACTATE LEVELS & MORTALITY RATE

• Sharpiro et al showed that increases in lactate level are associated with proportional increases in the mortality rate.
• Mikkelsen et al showed that intermediate levels and high levels of serum lactate are associated with increased risk of death independent of organ failure and shock.
• Random trials of patients with septic shock who present to the ED with hypotension and a lactate level higher than 2 mmol/L had a significantly higher in-hospital mortality rate than those who presented with hypotension and lactate level less than 2 mmol/L.
HYPERLACTATEMIA

• Elevated lactate levels can be the result of the following 3 reasons:
  1) Increased lactate production
  2) Decreased clearance of lactate
  3) Both of the above conditions happening simultaneously
INCREASED LACTATE PRODUCTION

• For a healthy individual, the liver and kidneys can remove lactate rapidly where a rise in lactate levels is only seen momentarily.
• For example, oxygen is essential for pyruvate oxidation.
• Any condition that deprives tissues of oxygen can lead to increased production of lactate.
• This lactate will then accumulate in the blood at a faster rate than it can be removed by the liver and kidneys.
DECREASED LACTATE CLEARANCE

• This problem becomes compounded by acidosis because the capacity of the liver to remove lactate from the circulation (60% to 70% of lactate is removed by the liver) is pH dependent.
• All acids produced within the body release hydrogen ions which reduced the pH of the blood and all bodily fluid levels.
• The more acidotic the circulation becomes, the less effective the liver becomes at removing the lactate.
RENAL COMPENSATION

• Acidosis enhances kidney uptake of lactate (excreting lactate through the urine).
• Also kidneys retain bicarb, reintroducing it back into the circulation to maintain the pH.
• This can only account for around 50% of hepatic loss and acidosis will quickly overcome bicarb and other buffer systems producing an acidosis.
LACTIC ACIDOSIS

• A blood lactate level > 5.0 mmol/L in combination with a pH < 7.35.
• Clinical signs include: tachycardia, tachypnea, AMS (confusion to coma), Kussmaul’s respiration
**SAMPLING REQUIREMENTS**

- Blood samples should be drawn without tourniquet (falsely increases lactate levels) from a artery or vein (in rare cases spinal tap to sample CSF may be necessary)
- Tubes must contain fluoride
- Must be processed quickly (within 15 minutes), lactate levels increase due to continue production after sampling. Increases by 30% in 30 minutes.
- If not place sample on ice to minimize changes
Every acid the body produces releases a H\(^+\) ion which produces an acidic environment within the body.

This can produce a Lactic Acidosis.

Differentiating the cause of increased lactic levels are key before a treatment plan can be implemented.

Lactic acidosis can be classified into two categories: Type A Lactic acidosis & Type B Lactic acidosis depending on the cause of hyperlactatemia.
TYPE A LACTIC ACIDOSIS

- An acute, life-threatening critical illness
- Due to tissue hypoxia and hypoperfusion
- Occurs when there is a mismatch between oxygen delivery and consumption, with resultant anaerobic glycolysis.

**Causes include:** Septic shock, Cardiogenic shock, Hypovolemic shock, Obstructive shock, regional ischemia (limb, mesenteric), seizures, shivering, severe anemia, severe hypoxemia or respiratory failure, COHb poisoning
TYPE B LACTIC ACIDOSIS

- Occurs in a variety of conditions (not due to hypoxia and hypoperfusion)
- Occurring in the context of normal tissue perfusion and adequate global tissue oxygenation.
- Gluconeogenesis (which takes place in liver and kidneys) is inhibited by the factors below.
- **Causes include**: liver disease, malignancy, medications (epinephrine), TPN, HIV infection and treatment, thiamine deficiency, mitochondrial myopathy, trauma, excessive exercise, diabetic ketoacidosis, ethanol intoxication, deficiency of specific enzymes involved in lactate metabolism (G6PD, fructose-1, pyruvate dehydrogenase deficiency) referred to as congenital lactic acidosis,
TYPE B LACTIC ACIDOSIS

• **Biguaniides** are a class of blood glucose-lowering drugs used in the treatment of diabetes.

• **Metformin**, most widely prescribed has been linked lactic acidosis (due to its ability to impair the function of the liver and kidney)

• Cyanide, cocaine, simvastatin, salicylates, theophylline, antiretroviral drugs, acetaminophens, are also linked to type b lactic acidosis.
HOW TO APPROACH AN ELEVATED LACTATE LEVEL
An elevated lactate level should prompt an evaluation for causes. This will help to determine the type of lactic acidosis that is present.

Decreased oxygen delivery due to systemic low-flow state, severe anemia, or regionally decreased perfusion.

If tissue hypoxia is ruled out after an exhaustive workup, consideration should be given to causes of hyperlactatemia without concomitant tissue hypoxia (type B lactic acidosis).
TREATMENT FOR TYPE A LACTIC ACIDOSIS

• The underlying mechanism of elevated lactate levels will determine the treatment pathway.
• Treatment is related to optimizing oxygen delivery via giving fluids or PRBC’s
• Increasing oxygen concentration
• Providing circulatory and pump support via vasopressors, along with inotropic agents.
OXYGEN SUPPORT

• Titrate FIO$_2$ according to PaO$_2$ obtained from the ABG.
• As long as the pH does not reflect an acidosis that may require the use of an artificial airway and mechanical ventilation, the use oxygen devices (nasal cannulas, simple mask, non-rebreathers) are fine.
• Devices that provide fixed or precise FIO$_2$ levels and high flow ranges are needed (Venti mask, HFNC, BiPAP).
• Improves cardiac output which will ultimately improve oxygen delivery
• In many cases, fluid resuscitation alone may be enough to restore hemodynamic stability, improve tissue perfusion, and reduce elevated lactate concentrations.
• Fluid use needs to be monitored or avoided in patients suffering from septic shock (associated with high mortality rate) and cardiogenic shock (leads to pulmonary edema).
• Provide fluid only until patient is no longer preload dependent.
Despite years of research, controversy persists about whether crystalloids or colloids are better for resuscitation.

Randomized trials in heterogeneous ICU patients have not detected differences in 28-day mortality rates between those allocated to crystalloids or 4% albumin.

**Hydroxyethyl starch** should not be used for fluid resuscitation in the ICU (higher mortality rate and acute kidney failure has been seen with its use).
CIRCULATORY & PUMP SUPPORT

• When signs of **hypoperfusion** is present, despite preload optimization or ongoing fluid administration the need for vasopressors and inotropic agents are necessary.

  • **Vasopressors** are used to increase systemic vascular resistance.
  • **Inotropes** are used to improve cardiac output and oxygen delivery.
VASOPRESSORS

- **Dopamine** and **norepinephrine** have traditionally been preferred initial vasopressors for patients with shock.
- Recent studies have shown higher mortality rates in patients with septic shock when dopamine was used.
- Norepinephrine is the initial vasopressor of choice for most types of shock.
- **Epinephrine** (known to increase lactate concentrations in skeletal muscles) is reserved for patients with refractory shock and low cardiac output.
• **Phenylephrine**, pure vasoconstrictor should be avoided in low cardiac output states. Best reserved for patients who develop a tachyarrhythmia on norepinephrine.

• **Vasopressin**, also a pure vasoconstrictor should also be avoided in low cardiac output states. Works great when added to existing norepinephrine therapy.
OPTIMIZING OXYGEN DELIVERY

- Cardiac output is the critical determinant of oxygen delivery.
- CO is augmented by ensuring adequate preload by fluid resuscitation or by giving inotropes or vasopressors.
- Monitoring $S_vO_2$, CVP, and hematocrit levels is the reasonable approach to determining when to introduce inotropes to improve cardiac output.
- An $S_vO_2$ below 70% despite adequate fluid resuscitation (CVP $\geq$ 8mmHg) and hematocrit levels higher than 30%, the inotrope of choice is dobutamine (short half-life makes it easy to titrate and less hypertension).
USING LACTATE LEVELS AS A GUIDE TO THERAPY
LACTATE LEVELS

• Lactate may be a useful marker for determining whether organ dysfunction is present and what course of therapy should be given.
• Serum lactate levels higher than 4 mmol/L has been used as a trigger to start aggressive resuscitation in patients, especially with sepsis.
• Measure lactate levels every 2 hours for the first 8 hours of resuscitation for patients with Type A lactic acidosis.
• Regards the approach taken, decrease lactate levels can be interpreted as an adequate response to the interventions provided.
RESUSCITATION END POINT

- $S_vO_2 \geq 70\%$ (never use this indicator alone due to severe sepsis and septic shock producing elevated $S_vO_2$)
- Lactate clearance of 10% or more (preferably 20%) within the first 6 hours after presentation
Lactate $\geq 4.0$ mmol/L

**Type A lactic acidosis** (shock, regional ischemia)

- **Fluid-responsive?**
  - Yes: Give fluids (crystalloids or colloids)
  - No: 
    - **ScvO$_2 \geq 70\%$?**
      - Yes: Consider vasodilators if hemodynamically stable
      - No: Optimize oxygen delivery
    - **If hypoxemic**
      - Increase arterial oxygen saturation to $> 92\%$
    - **If anemic**
      - Increase hemoglobin to $\geq 7.0$ g/dL ($\geq 10$ g/dL with cardiac ischemia)
    - **If myocardial dysfunction**
      - Consider inotropes
    - **If increased oxygen demand**
      - (pain, agitation, dyssynchrony)
      - Treat underlying cause

**Type B lactic acidosis** (eg, due to liver disease, medications, malignancy)

- Treat underlying cause

Recheck lactate
TREATMENT FOR TYPE B LACTIC ACIDOSIS

• Since the goal is not to correct mismatches in oxygen consumption and delivery, treating Type B lactic acidosis is quite different.

• Treatment needs to be centered around eliminating the cause (ex. Treat malignancy, discontinue offending medications).

• This will eliminate the harmful effects of acidosis (negative inotropic effect).
TREATMENT FOR TYPE B LACTIC ACIDOSIS

• Renal replacement therapy has shown some success in drug-induced lactic acidosis.

• L-carnitine has had promising results in treating patients with HIV (carnitine plays a vital role in mitochondrial function and these patients are carnitine-deficient).

• Antioxidants (coenzyme Q10, vitamin C & E) and amino acids (L-arginine) treat mitochondrial disorders.

• Thiamine and biotin deficiencies can occur in patients receiving TPN without vitamins and in alcoholics. These nutrients should be supplemented accordingly.

• Sodium bicarb, carbicarb, tromethamine, dichloroacetate has been used in the management of Type B lactic acidosis, but with little success.
REFERENCES

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THE END
ANY QUESTIONS?