Hell or High Lactate

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Positive troponin?
Inpatient or Observation?
Lactate elevated?
Goals

• What causes lactate production?
• Does it prognostic anything?
• Should lactate guide resuscitation?
Goals

• What causes lactate production?
  Catecholamines, Aerobically

• Does it prognostic anything?
  Yes

• Should lactate guide resuscitation?
  Probably not
Lactate Production

• It is not a “waste product” of anaerobic metabolism

• It is an important energy shuttle
Normal Metabolism

- Lactate production arises mainly from skeletal muscle (25%), skin (25%), brain (20%), intestine (10%), and erythrocytes (20%).
- Glycolysis metabolizes glucose to pyruvate.
- Under aerobic conditions, pyruvate is converted to Acetyl-CoA which enters the Krebs cycle to produce ATP by oxidation.
Glucose $\xrightarrow{PFK}$ Pyruvate $\xrightarrow{LDH}$ Lactate

$\text{NADH} + H^+ \xrightarrow{} \text{NAD}^+$

$\text{PDH} + \text{thiamine} \text{ diphosphate}$

Mitochondrion

Acetyl CoA $\xrightarrow{}$ Krebs Cycle $\xrightarrow{}$ ATP
Normal Metabolism

- Pyruvate is also in equilibrium with lactate in the cytosol
- Bidirectionally catalyzed by LDH
- This requires NADH and H+
- Normal lactate:pyruvate ratio of approximately 10:1.
Glucose $\xrightarrow{PFK}$ Pyruvate $\xrightarrow{LDH}$ Lactate

$\text{PDH} + \text{thiamine diphosphate}$

Mitochondrion

Acetyl CoA $\xrightarrow{\text{Krebs Cycle}}$ ATP
Normal Metabolism

- There is also a glycolytic component that occurs in the cytosol.
- Compliments the oxidative pathway.
- Beta2-adrenergic stimulates cAMP inducing glycogenolysis and glycolysis for ATP production.
- Pyruvate is a byproduct.
- \( \text{Na}^+ / \text{K}^+ - \text{ATPase} \) pump uses the ATP for much of the cellular work.
Garcia-Alvarez et al. Critical Care 2014 18:503
Lactate Clearance

- Consumption by local or distant mitochondria for energy production
  - Via pyruvate and Krebs cycle
- Utilized as substrate for gluconeogenesis
  - Cori cycle
- Metabolism occurs in the liver (60%) and kidney (30%)
- Urinary excretion threshold is 5-6 mmol/L
Abnormal Lactate Production

- Leukocytes also generate lactate during phagocytosis or when activated in sepsis.
- The lungs can create lactate during acute lung injury without tissue hypoxia.
- Accelerated glucose production in inflammatory lung tissue.
Abnormal Lactate Production

• Anaerobic metabolism in hypoxic tissue

• Pyruvate cannot enter the Krebs cycle, so it is shunted to lactate
Increased Glycolytic Flux

- Severe exercise
- High work of breathing
- Catecholamine administration
- Sepsis
- Maintains normal lactate:pyruvate ratio if adequate oxygen
Impaired Clearance

- Elevated reducing environment (high NADH)
- Ketoacidosis
- Ethanol ingestion
Hyperlactatemia

- Abnormal lactate/pyruvate ratio
- Occurs if pyruvate is prevented from entering Krebs cycle
  - Hypoxia (already mentioned)
  - Amount exceeds capability of mitochondria (excessive glycolytic flux)
  - Mitochondrial dysfunction (sepsis induced cytokines)
  - Thiamine deficiency
Glucose $\xrightarrow{PFK}$ Pyruvate $\xrightarrow{LDH}$ Lactate

$\text{NADH + H}^{+} \rightleftharpoons \text{NAD}^{+}$

PDH + thiamine diphosphate $\rightarrow$ Mitochondrion

Mitochondrion $\rightarrow$ Acetyl CoA $\rightarrow$ Krebs Cycle $\rightarrow$ ATP
Tissue Hypoxia Myth

• In sepsis, lactate is NOT produced by anaerobic metabolism
  • Septic patients have hyperdynamic circulation
• Mt Everest Climbers (PaO₂ 24, lactate normal)
• Oxygen delivery to tissues is adequate
  • \( P_{a\,O_2} 100, P_{v\,O_2} 40, P_{cytosol\,O_2} 5 \)
  • But Mitochondrial threshold is 1
• Critical oxygen delivery occurs at 3.8 mL/kg/min (CO 1.8 L/min)
• Studies trying to correct oxygen delivery fail to improve
Acidosis Production

- Glycolysis to pyruvate produces H+, pyruvate to lactate consumes H+
  - Stoichiometrically does not generate any net protons
  - But lactic acid by p-chem must generate acidosis
  - The key is that protons are consumed by a fully functional Krebs cycle that can keep up
Acidosis Production

- Hyperlactatemia without acidosis can persist as long as there is not a decreased Krebs cycle flux.
- Acidosis generated by production of lactate occurs when lactate:pyruvate ratio is altered by failure of Krebs cycle.
• Lactate:Pyruvate Alteration besides Hypoxia

  • Impaired Tissue Extraction
    • Microcirculatory dysfunction (vasodilation)
    • Inflammatory changes to endothelium
    • Regional and microregional oxygen delivery does not meet demand
    • Microthrombotic occlusion
  • Mitochondrial dysfunction
  • Diminished clearance -- Hepatic dysfunction
  • These don't improve with increased cardiac output or tissue oxygen perfusion.
Excessive Glycolytic Flux

- Lactate in septic shock produced by beta-2 adrenergic stimulation
- Endogenous catecholamines stimulate beta-2 receptors
- This upregulates glycolysis, generating pyruvate
- Pyruvate is generated in excess of mitochondrial capability to use in the TCA cycle
- Excess pyruvate is converted into lactate--changing ratio
- This is entirely aerobic
Lactate might be compensatory

- Lactate is not a toxin
- Lactate serves as efficient metabolic fuel for heart and brain in stress
- Depletion of lactate caused cardiovascular collapse
- Cardiac myocytes use lactate as fuel in some circumstances, such as during exercise, beta-adrenergic stimulation, and shock.
- Giving lactate has been shown to improve outcomes in CAB and HF patients
Measuring lactate

- Arterial and venous samples are good
- Avoid long tourniquet times
- On ice is preferred if processing time exceeds 15 min
- Leukocyte and Erythrocyte metabolism
Prognostic value of lactate

• Lactate is a marker for sepsis and badness

• Like sinus tachycardia

• Lactate as marker of critical illness and metabolic stress
Identification of Occult Shock

- Autonomic system and endogenous catecholamine response are variable
- Some patients have a weak response and immediately develop hypotension
- Other patients have a robust response supporting their blood pressure and thereby preventing hypotension
  - Deceptively reassuring vital signs
  - But they are in a catecholamine dependent shock state
  - These patients have an increased risk of decompensation and death
- Lactate is ultimately a marker of catecholamine release
Identification of Occult Shock

• This makes it useful for detection of occult shock

• Hyperlactatemia is correlated with increased mortality regardless of etiology

• Sepsis-induced hypotension has a much better prognosis than septic shock with a lactic acidosis
- Lactate level of 4 mmol/L
  - Used by Surviving Sepsis Campaign as arbitrary threshold for identifying cryptic shock
  - Lactate has a continuous curvilinear association with mortality
  - There is no clear elevation that is evidently safe
  - Intermediate concentrations (lactate 2-4) or even high-end normal range (1.4-2.3) still indicated a poorer prognosis than normal lactate concentrations
Lactate Clearance as marker of adequate resuscitation

- Rivers trial established EGDT in severe sepsis and septic shock
  - NEJM 2001
- Used proprietary designs continuous ScvO2 as a target to assess than oxygen delivery was adequate
- Intermittent measurement of ScvO2 correlated well
Lactate Clearance

• Jones studied RCT of lactate clearance vs ScvO2
  • No difference between the two
  • 10% Clearance threshold
• Averaging out of ScvO2 is misleading
  • Even if there is tissue hypoperfusion
  • Following ScvO2 results in mismanagement.
Lactate Clearance

- Lactate clearance has repeatedly been shown to independently predict survival from sepsis.
- This is not true of SvO2 (as a single variable)
Lactate Clearance

• Lactate is a test, and it holds the false promise of simplifying clinical decision making to a numerical value, one that you can order, even from afar.
Lactate Clearance

• We don't know if directing therapy at clearing lactate improves outcomes

• When looked at separately, clearing they do not alter outcomes
  • ARISE, ProCESS studies

• Lactate as a marker for hypoxemia caused by hypoperfusion is false therefore trending it or using interventions ie fluid boluses to bring it down is devoid of evidence, which is important especially in an age where doctors live behind a screen and worship numbers on that screen.
What to Do

• Source control
• Antibiotics
• Reasonable amount fluids
• Vasopressors
• Reasses

• Use lactate along with ScvO2, echo, VaCO2 difference, mental status, urine output, mottling
What if lactate is not clearing?

• It is not telling us that we did not fix anaerobic metabolism
• You need functioning liver and kidney
• Do nothing empirically
What if lactate is not clearing?

- If left ventricular dysfunction — give inotrope
- Low Cardiac Output
- Assess volume — give volume
- If Hgb low — give blood
- Look for ischemic/infarction tissue (ie regional lactate production)
  - Bowel ischemia/infarction
  - Limb arterial occlusion
  - Compartment syndrome
What if lactate is not clearing?

- Consider thiamine if malnourished to maximize aerobic metabolism
- Limit beta-adrenergic stimulation
  - Vasopressor choice
    - Esmolol
- Reduce skeletal muscle work
  - Mechanical ventilation for work of breathing
  - Paralytics
- Avoid hepatotoxins
Reference and Outline available at:
resusreview.com/RegionsMar17